The purpose of environmental monitoring is to portray accurately typical workplace exposures, which requires sampling workers with the highest exposure risks (7). All monitoring—active and passive—must meet OSHA's accuracy requirements of ±25% at 1 ppm and ±35% below 1 ppm (7). Passive monitoring is performed by personal dosimetry badges worn by employees. These badges, which must be developed before results can be quantified, are designed to indicate the amount of ethylene oxide absorbed. Personal dosimeters have an advantage over active sampling in terms of cost and reduced complexity (22). However, conflicting data exist regarding the ability of passive dosimetry accurately to meet OSHA's regulations of a 1-ppm PEL and a 0.5-ppm action level (23). Passive dosimeters that meet OSHA's monitoring standards have been designed (23). Errors in passive dosimetry monitoring can occur owing to interference when the dosimeter is worn in direct sunlight or is worn for less than 8 hours (23). In addition, the capacity of the dosimeter can be exceeded by concentrations of ethylene oxide greater than 9.9 ppm (23).

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CHAPTER 105
Aromatic Solvents

John B. Sullivan, Jr., and Mark D. Van Ert

Aromatic solvents are benzene derivatives with high vapor pressures and low boiling points that increase with increasing molecular weight. These solvents possess high vapor densities and are not very water soluble. Most of these compounds are used as starting chemicals or intermediate chemicals for synthesis of other organic compounds. Aromatic solvents are used also in myriad occupations and industries, in paints, lacquers manufacturing, resins, pharmaceuticals, printing, glues and adhesives, degreasing operations, electronics, and rubber manufacturing (1).

Commonly used aromatic compounds include toluene, benzene, xylene, styrene, ethylbenzene, monochlorobenzene (MCB), and trimethylbenzene (Fig. 105-1). Benzene is discussed in a separate chapter (see Chapter 59).

Most commercial aromatic solvents have a boiling point not much lower than 0°C or higher than 200°C (1). If the boiling point of a solvent is too high and the vapor pressure too low, separating the solvent from the material it is used to dissolve would be difficult. Therefore, most organic solvents are liquid at room temperature.

Aromatic solvents are characterized by nonpolarity and high lipid solubility. These solvents frequently are used in mixtures in occupational settings, such as combinations of toluene, benzene, styrene, ethylbenzene, trimethylbenzene, and xylene. Naphthalene, although an aromatic compound, is not a solvent; rather, it is a white, crystalline solid used as a repellent for moths, and it volatilizes easily.

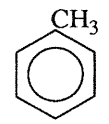
Aromatic solvents are derivatives of coal and petroleum refining. When coal is heated in the absence of air, it is broken down into volatile compounds consisting of coal gas and coal tar. The residue of this process is termed *coke*.

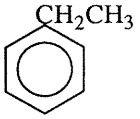
The distillation of coal tar results in the production of aromatic compounds such as benzene, toluene, xylenes, phenols, cresols, and naphthalene. Aromatic compounds can also be produced by catalytic processes in which aliphatic hydrocarbons are employed at high temperatures and high pressures to dehydrogenate the compounds and form cyclic structures of the aromatic hydrocarbons.

FACTORS INVOLVED IN SOLVENT TOXICITY

Exposure to aromatic solvents occurs through contact with vapor or liquid, the main routes of absorption being pulmonary and dermal. The toxicity of a solvent relates to a combination of its physiochemical properties, inherent toxicity, metabolites, and clinical pharmacokinetics. For solvents, such as benzene and styrene, metabolites are the primary toxins. Toxicity factors can be summarized as follows:

- Toxic nature of parent compound
- Toxic nature of metabolites
- Target organs and target tissues
- Interaction with other solvents or drugs


Toluene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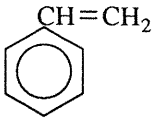
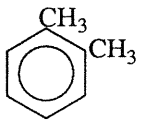
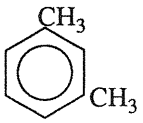
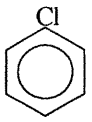
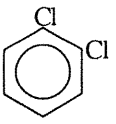

Styrene

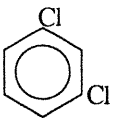

o-Xylene

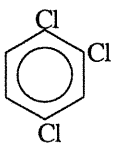

m-Xylene

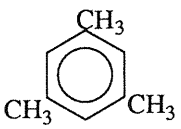

p-Xylene

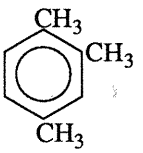

Monochlorobenzene


1,2-Dichlorobenzene


1,3-Dichlorobenzene


1,2,4-Trichlorobenzene


1,3,5-Trimethylbenzene


1,2,4-Trimethylbenzene

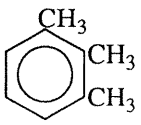

1,2,3-Trimethylbenzene

Figure 105-1. Common aromatic solvents.

- Influence of prior disease states
- Exposure (dose, duration, intensity)
- Solvent physiochemical characteristics (vapor pressure, vapor density, reactivity)
- Routes of exposure [pulmonary, dermal, gastrointestinal (GI)]

Solvent Vapor Pressure and Vapor Hazard Index

The vapor pressure of a solvent is an important health aspect that is directly related to its airborne concentration and, therefore, to its potential for exposure and toxicity. This concept is known as the *vapor hazard index* (VHI) of a solvent.

Vapor pressure is defined as the force per unit area exerted by molecules of a vapor that is in equilibrium with a liquid or solid (2). Vapor pressure is expressed in terms of millimeters of mercury in relation to atmospheric pressure (1 atm = 760 mm Hg) and directly relates to the concentration of solvent in the breathing zone of exposed individuals. The vapor pressure of a solvent obeys the same physical laws as do other gases: $P_v = nRt/V$, where P_v = vapor pressure (expressed as millimeters of mercury); n = moles; V = gas volume (expressed as cubic meters); R = gas constant (6.236×10^{-5}); and t = absolute gas temperature (in degrees Kelvin).

Rearrangement of this formula yields an equation that allows for calculation of the vapor concentration from the vapor pressure of a gas that is in an equilibrium state:

$$P_v = \frac{nRt}{V} = \frac{CRt}{MW} = x(\text{atm})(2 \times 10^{-6})$$

where C = concentration (expressed as millimeters per cubic meter); MW = molecular weight (expressed in daltons); x = concentration [expressed as parts per million (ppm)]; atm = 760 mm Hg.

The vapor hazard ratio of solvents can be compared by this method to help to determine the potential of human exposure. The formula expresses the vapor pressure in terms of an equilibrium state, or worst-case scenario, as would be achieved in a closed environment. Solvents or chemicals with the same

threshold limit value (TLV) or permissible exposure limit (PEL) may present two distinctly different health hazards owing to their different vapor pressures. Such a relationship is expressed by the VHI of the individual chemicals. Two related examples of VHI follow:

Chemical A: TLV = 0.02 ppm
Vapor pressure = 0.00014 at 25°C
Chemical B: TLV = 0.02 ppm
Vapor pressure = 0.00001 at 25°C

Rearranging this equation allows for a calculation of the saturated vapor concentration in parts per million of a vapor in an equilibrium state (V_{peq}):

$$V_{peq} = P_v \times \frac{1 \times 10^6}{\text{atm}}$$

The equilibrium vapor pressure, as calculated using the preceding formula, can be used to calculate the VHI:

$$\text{VHI} = \frac{\text{Equilibrium vapor pressure (ppm)}}{\text{TLV (ppm)}}$$

The greater the VHI, the greater is the potential hazard for inhalation and dermal contact (1).

$$\text{Chemical A: } V_{peq} = \frac{(1.4 \times 10^{-4})(1 \times 10^6)}{760 \text{ mm Hg}} = 0.184 \text{ ppm}$$

$$\text{Chemical B: } V_{peq} = \frac{(1 \times 10^{-5})(1 \times 10^6)}{760 \text{ mm Hg}} = 0.0132 \text{ ppm}$$

$$\text{Chemical A: VHI} = \frac{0.184 \text{ ppm}}{0.02 \text{ ppm}} = 92$$

$$\text{Chemical B: VHI} = \frac{0.0132 \text{ ppm}}{0.02 \text{ ppm}} = 6.6$$

Chemical B would present less of a hazard than chemical A in terms of vapor exposure:

$$\text{VHI}\left(\frac{\text{chemical A}}{\text{chemical B}}\right) = \frac{92}{6.6} = \frac{13.9}{1}$$

Dose, Exposure, and Target Organ Toxicity

The predominant target organs for aromatic solvents are the nervous system, liver, kidneys, skin, lungs, and mucous membranes of the airways and eyes. Benzene's main target organ is the hematopoietic system. Target organ toxicity of solvents can be categorized as neurologic (peripheral, central, neurobehavioral); hepatic; renal; dermal (contact and allergic); pulmonary (acute and chronic bronchitis, bronchial hyperresponsiveness, airway irritation, and mucous membrane inflammation); upper airway (mucous membrane irritation, vocal cord irritation); and ocular toxicity (irritation).

Clinical effects of exposure depend on the inherent toxicity of the solvent, the exposure concentration, absorbed dose, length of exposure, toxic metabolites, preexisting medical conditions, and route of exposure. Exposure to multiple solvents is a common occupational hazard.

Owing to the vapor hazards of aromatic solvents, inhalation is the most common route of exposure. However, dermal absorption via contact with vapors or liquids can contribute to or cause toxicity. Chemicals that have the potential for dermal absorption or for dermal toxicity are labeled with a "skin" notation by the American Conference of Governmental Industrial Hygienists (ACGIH) (3).

TABLE 105-1. Summary of aromatic solvent toxicity

Acute exposure	Chronic exposure
Dizziness	Fatigue
Euphoria	Headache
Confusion	Nausea
Agitation	Neurobehavioral disturbances
Syncope	Cerebral atrophy
Cardiac dysrhythmias	Confusion
Coma	Dementia
Ocular irritation	Cognitive decline
Respiratory irritation	Memory loss
Headache	Cerebellar signs
Liver damage	Ataxia
Renal damage	Neuropsychological damage
	Liver damage
	Renal damage

Aromatic solvents vary with respect to skin penetration. Factors that increase skin penetration include injury, high moisture content, surface area of exposure, anatomic part, and duration of contact. Other important factors directly relating to increased absorbed dose of a solvent exposure are physical exercise and respiratory rate. Physical exercise and increased respirations will result in an increased absorbed dose of solvent vapors. Coingestion of ethanol inhibits the metabolism of some solvents and will result in higher blood levels. Coexposure to other solvents will result in competition for enzymatic sites and decrease metabolism of solvents. These factors influence the results of biological monitoring and toxicity.

Solvents may produce acute, reversible neurotoxic changes or permanent neuropathology, again depending on the solvent, dose, exposure time, and metabolism. Table 105-1 summarizes the acute and chronic effects of aromatic solvent exposure. Acute inhalational exposure to high airborne concentrations can produce dizziness, syncope, confusion, euphoria, respiratory irritation, and in some instances, coma (4,5). Acute and chronic exposure to toxic concentrations from inhalational solvent abuse may cause neurobehavioral disturbances, cerebral atrophy, cerebellar dysfunction, dementia, and permanent neuropsychological dysfunction. Such is the case with toluene (4,5).

Toxic neuropathy due to aromatic solvent exposure is confined primarily to the central nervous system (CNS). Only isolated case reports indicate the potential for peripheral neuropathy. The term *toxic encephalopathy* is used to describe permanent residual neurocognitive defects and neurologic impairment. Some limited evidence reveals that aromatic solvents also can cause peripheral neuropathy. However, occupational exposure is usually to a mixture of solvents and, therefore, relating clinical effects to a specific agent can be difficult.

Organic solvents tend to be lipophilic, thus favoring distribution to tissues high in lipid content, such as the brain and liver. In general, the more lipid solvents are metabolized to more polar metabolites, which reduces their ability to penetrate across biological membranes. Overall, solvent metabolism involves two phases by the cytochrome P-450–dependent monooxygenase system: The first phase consists of introduction of a polar group or unmasking of a polar group by oxidative, reductive, or hydrolytic reaction. The second phase consists of conjugation with glucuronic acid, sulfate, or glutathione. The liver is the main metabolic organ, but other sites of P-450 metabolism are the kidneys, lung, skin, olfactory epithelium, and nasal epithelium.

Excretion of unchanged solvent occurs mainly via the lungs. Excretion of metabolites occurs primarily in the urine. In some instances, volatile metabolites are exhaled by the lungs. More lipid solvents exhibit multiple phases of elimination: a rapid

removal from the blood to lipid compartments and then a slow elimination phase from lipid storage sites.

DIAGNOSTIC APPROACH TO SOLVENT NEUROTOXICITY

Diagnosing a neurologic disease caused by solvent exposure requires obtaining a careful history inclusive of occupational and environmental exposures and performing a neurologic examination and tests to confirm the suspected diagnosis. The neurologic examination should note specific signs and symptoms related to mental status, motor tone and function, strength, sensory function, gait, posture, reflexes, cranial nerve functions, cognition, speech functions of the cortex, the basal ganglia, the midbrain, the brainstem, and the spinal cord. Aside from the usual clinical laboratory tests and biological markers of exposure, specific neurologic tests from which to select include neurophysiologic assessments [nerve conduction studies and electromyography (EMG)], electroencephalography (EEG), evoked potentials, neuroimaging, and neuropsychological tests. Neurologic tests reported to be abnormal in cases of solvent toxicity include the electroencephalograph, cerebral blood flow studies, magnetic resonance imaging (MRI) and computed tomography (CT) scans, nerve conduction velocities (NCVs) and EMG, evoked potentials, and neuropsychological tests (6–10). However, some published studies suffer from a lack of controls and fail to show an association between chronic low-level solvent exposure and neurotoxicity (11–14).

Neuropsychological Testing

Chronic occupational exposure to organic solvents has been reported in some studies to result in abnormal neuropsychological effects, referred to as the *solvent syndrome* (6–15). However, there is disagreement regarding the verification of this solvent syndrome (5,11,15–26). Studies have failed to demonstrate an association or dose-response relationship between chronic low-level exposure to organic solvents and a psychoorganic brain syndrome (11). Those studies that support a low-level exposure solvent-induced psychoorganic syndrome have been criticized for their lack of controls, multiple unaccounted-for environmental exposures, retrospective nature of the study, and lack of objective evidence of CNS neurologic damage (4). One controlled study of individuals with a diagnosis of toxic encephalopathy from chronic solvent exposure did not demonstrate, by CT scanning, any difference in cerebral atrophy between patients and controls (26).

However, most published studies of the solvent-induced psychoorganic syndrome have relied on neuropsychological testing, which is generally accepted as being more sensitive for detecting early behavioral dysfunction caused by CNS neurotoxins as compared to routine neurologic examinations, MRI, and CT scanning (27,28). Although experts widely accept that neuropsychological methods are sensitive indicators of brain dysfunction, many variables and confounding factors must be taken into account: cultural differences, premorbid status, prior disabilities, demographic variables, age, alcohol use, education, prior intellectual function, mood changes, personality, drug use and abuse, and head injury (27,28). These variables have a strong influence on the outcome of neuropsychological testing.

To be of value, neuropsychological studies must be performed by a qualified neuropsychologist experienced in testing patients with neurotoxic exposures. An appropriate testing battery must be used that is sufficiently sensitive and specific to detect the effects of neurologic toxins. Properly performed neuropsychological testing must characterize a patient's preexisting neurocognitive status and provide evidence of the presence of psychiatric disorders, depression, stress, and premorbid cognitive state.

Neuropsychological impairments secondary to toxic exposure may involve the following functional areas, which can be tested by appropriate methods (29): attention, function, visuospatial skills, learning, short-term memory, mood, fluency (verbal or visual), motor abilities, adjustment, and intelligence. Published studies linking low-level solvent exposure with abnormal neuropsychological test findings suggest that chronic low-level exposures in occupational settings are associated with cognitive changes, abnormal reaction times, short-term memory problems, and abnormal visuospatial functions. Verbal and nonverbal reasoning seem not to be affected (28). However, whereas most authorities agree that acute intoxication from high levels of organic solvents can cause toxic encephalopathy, dizziness, confusion, headache, CNS depression, lethargy, and incoordination, the effects of low-level chronic exposure remain controversial. Because of the continued controversy surrounding the psychoorganic syndrome and chronic solvent exposure, the World Health Organization proposed a categorization relating to the degree of impairment (Table 105-2) (4).

Solvent neurotoxicity must also be discerned from other neurologic diseases. For example, Alzheimer's disease is associated with decline in language abilities, visuospatial skills, and memory function (30). Patients with solvent-induced neurotoxicity may also demonstrate visuospatial difficulties and memory deficits. However, Alzheimer's disease is associated with language dysfunction, whereas solvent neurotoxicity is not. In addition, individuals with chronic neurotoxicity secondary to solvent exposure tend to remain the same or improve over time once the exposure has terminated. In contrast, patients with Alzheimer's disease generally will show neuropsychological decay over time (30). Solvent-toxic individuals may have problems with attention and tracking as well as visuospatial processing and short-term memory. This is consistent also with an Alzheimer's diagnosis. However, retention of language, writing, and reading skills is more clearly indicative of solvent toxicity than of Alzheimer's disease.

The intelligence quotient (IQ) of an individual can be affected after toxic exposure to a solvent and in Alzheimer's disease. However, with solvent exposure, IQ deterioration terminates after discontinuation of exposure, whereas in Alzheimer's disease, IQ deterioration can continue. Intact reading and writing abilities favor solvent-induced neurotoxicity. Progression of cognitive decline in the absence of exposure favors a diagnosis of dementia such as Alzheimer's disease. Once solvent exposure is terminated, cognitive function usually remains stable or improves in patients with solvent-induced neurotoxicity.

TABLE 105-2. World Health Organization solvent impairment categories

Type 1	Complaints of nonspecific symptoms only, which are reversible if exposure is terminated.
Type 2A	Sustained personality or mood change symptoms not reversible on discontinuation of exposure.
Type 2B	Intellectual function impairment with objective signs and evidence of impairment on neuropsychological tests. Possible presence of minor neurologic signs that are not reversible.
Type 3	Dementia and marked global deterioration in intellectual function and positive neurologic signs that are poorly reversible and nonprogressive once exposure ends.

Adapted from ref. 4, with permission.

Neurophysiologic Testing

EMG and nerve conduction studies are used to evaluate peripheral nerve functions. EMG is employed to assess motor function and the integrity of the motor neuron, its axon, and the muscle cells it supplies. Before EMG results become abnormal, denervation of the motor unit must occur (4,29). EMG is a sensitive tool for detecting ongoing or previous axonal degeneration.

NCVs test the integrity of nerve fibers, cell body, and axon and its myelin sheath and can localize areas of impaired function (axonal dysfunction, demyelination, myopathy, or nerve atrophy). NCVs are sensitive to nerve demyelination changes but are insensitive to quantifying axonopathies. NCVs may remain normal if only a few fibers continue to conduct at velocities (4). Both EMG and NCV results may be normal in the early phases of a toxic peripheral neuropathy.

ELECTROENCEPHALOGRAPHY

EEG provides real-time monitoring of the brain's electrophysiologic activity (4,29). Brain dysfunction may appear as an asymmetry of EEG patterns, changes in wave amplitude, frequencies, and wave patterns. Some toxic solvent exposures can cause the EEG results to become abnormal. Neurodegenerative diseases may first appear with a normal EEG outcome; then, as the disease progresses, abnormal EEG slowing occurs (29). However, EEG generally is not sufficiently specific for diagnosing neurotoxic diseases.

NEUROIMAGING

Neuroimaging techniques include CT and MRI as the two standard methods by which to image CNS anatomic structures. Other, less frequently used methods are single-photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance spectroscopy.

CT and MRI have limited use in detecting neurotoxicity caused by solvents except in cases of high-dose exposure such as with intentional toluene inhalational abuse (4,29). CT and MRI of toluene abusers have revealed neuropathologic changes such as diffuse cerebral atrophy, cerebellar atrophy, brainstem atrophy, and loss of gray–white matter differentiation (4). However, in cases of low-level chronic occupational solvent exposure, CT has not proved capable of discerning healthy control subjects from individuals with symptoms (26).

SPECT scanning has been reported to have value in assessing neurotoxic effects of chemicals (31,32). Other researchers have reported no significant advantage of SPECT scanning in such cases (33). SPECT imaging reflects regional cerebral blood flow by measuring the uptake of a radiopharmaceutical (^{99m}Tc hexamethyl propyleneamine oxine) in blood and brain tissue. SPECT measures dynamic brain functioning by determining the metabolic process that removes radiolabeled tracers from blood. Thus, SPECT scanning remains a potential tool for assessing neurotoxicity but must be used and interpreted in light of other findings.

PET scanning also demonstrates cerebral function and elucidates CNS changes that are functional as opposed to anatomic. PET is expensive and requires specialized equipment. PET scanning may eventually become of diagnostic value in neurotoxic exposure diagnosis, but more studies of this method are required. PET tracers include ^{15}O-labeled water (for assessing cerebral blood flow), ^{18}F-fluorodeoxyglucose (for evaluating brain metabolism), and ^{18}F-fluorodopa (for assessing levels of dopamine receptor) (4).

EVOKED POTENTIALS

Evoked potentials are electrical cortical responses produced by the stimulation of specific afferent pathways and recorded through the scalp from the brain's surface. They are used to assess the integrity of CNS sensory pathways, and their use is limited in diagnosing neurotoxicity. Evoked potentials represent the integrity of electrical manifestations through multisynaptic pathway activity within the CNS and, thus, they can be used to screen the integrity of the synapses in the CNS (4,29). They include auditory evoked potentials, visual evoked potentials (VEPs), and somatosensory evoked potentials (SEPs). Currently, evoked potentials should be viewed as a limited screening tool for assessing the integrity of the receptor-to-cortex pathway.

VEPs examine the integrity of the optic system pathway from the optic nerve to the geniculate nuclei up to the calcarine cortex, following stimuli to the retina. Two forms exist: flash VEPs and pattern-shift VEPs. Each eye is tested separately. Normal latency is approximately 100 milliseconds (P100 peak).

Brainstem auditory evoked potentials are used to study neurodegenerative disease of the brainstem and demyelinating diseases such as multiple sclerosis. Noise stimuli are used to activate cranial nerve VIII pathways.

SEPs are assessed by stimulation of peripheral nerves, and findings are recorded over the sensory cortex via the dorsal column of the spinal cord to brainstem, thalamus, and cortex. Neurotoxins that affect peripheral nerves can cause these readings to be abnormal.

The use of evoked potentials as a diagnostic tool for neurotoxicity is limited, and results must be interpreted in light of other findings. Abnormal evoked potentials have been found in toluene-related toxic exposures involving inhalational abuse (34).

RESPIRATORY IRRITATION AND INFLAMMATORY EFFECTS OF AROMATIC SOLVENTS

The respiratory toxicity of solvents depends on the chemical and physical nature of the solvent, the concentration of the solvent inhaled, and the additive effects of solvents in mixtures. Respiratory toxicity is most apparent with high-level exposures. However, studies show that pulmonary injury is not limited to high-dose exposure but can occur at concentrations of multiple solvents below the U.S. Occupational Safety and Health Administration (OSHA) PELs (35).

Most solvents, including the aromatic solvents, are mucous membrane irritants and thus are irritants of the upper and lower respiratory tract. Tests of sensory irritation have demonstrated the irritant nature of toluene, xylene, ethylbenzene, and styrene (36,37). Studies performed in animals under controlled chamber conditions showed a qualitative correlation for eye, nose, and throat irritation experienced by humans from vapors of common solvents (36,37). However, these solvents were mixtures of aliphatic compounds and alcohols.

Both upper and lower respiratory symptoms have been reported in cases of individuals exposed to low-level volatile organic solvents. However, most case reports have included multiple solvents and thus have multiple confounding factors. Although it is generally accepted that high-level aromatic solvent exposure produces CNS effects and may also result in pulmonary toxicity, studies are showing that low-level exposures also can result in respiratory symptoms such as shortness of breath, cough, and chest tightness. Apparently, mixtures of volatile organic solvents tend to have additive effects.

In animal studies, the upper respiratory tract mucosae of rats showed inflammatory cell infiltration in the nasal cavity, trachea, and larynx when the rats were exposed to low concentrations of a mixture of paraffins, naphthenes, and alkyl aromatic hydrocarbons (38). Further low-level exposure of rats to xylene caused alterations in pulmonary membrane structures (39).

That both high-level and low-level exposure to aromatic solvents can cause bronchial hyperresponsiveness is documented in published case reports. Bronchial hyperresponsiveness is a reversible airway obstruction after physical, chemical, or pharmacologic stimuli. Its clinical presentation includes wheezing, cough, and shortness of breath on exercise or inhalation of cold air and irritants. Bronchial hyperresponsiveness may be present as a preexisting condition in individuals without respiratory symptomatology. Evidence points to an inflammatory process as the basis or underlying pathophysiologic mechanism of bronchial reactivity, which results in smooth-muscle contraction, airway edema, and stimulation of the nervous system, which in turn leads to symptoms (40).

Airway hyperresponsiveness as an acquired condition resulting from exposure to airborne irritants is substantiated by evidence. Bronchial reactivity has been defined as a 20% declination in the forced expiratory volume over 1 second (FEV_1). Some individuals have bronchial hyperresponsiveness yet can be asymptomatic and still have a 20% declination of their FEV_1 on methacholine challenge (40). Evidence for acquired airway responsiveness from irritant exposure comes from experimental studies, case reports, and epidemiologic studies (5).

Cellular changes described in bronchoalveolar lavage fluid from patients who demonstrate bronchial hyperresponsiveness include an increased number of desquamated epithelial cells, activated inflammatory cells, mast cells, and macrophages (41). Also, increased concentrations of inflammatory mediators are found in bronchoalveolar lavage fluid, indicating activation of these immune cells. Studies have shown that blood interleukin-8 production is increased in chemical workers with bronchitis symptoms (41). In these cases, bronchitis was diagnosed as productive cough after waking up, during smoking, or during the winter season. Chronic bronchitis was diagnosed if these complaints were present on most days for at least 3 months in the year for at least 2 successive years. The blood interleukin-8 level was significantly higher in workers with respiratory symptoms of the acute and chronic bronchitic variety as compared to workers without those symptoms. Once a person has developed reactive airways, exposure to a variety of unrelated airborne irritants may trigger symptoms (42–45). However, bronchial hyperresponsiveness is not the equivalent of reactive airways dysfunction syndrome (RADS). First described by Brooks et al. (46) in 1985, RADS is considered to be a subset of irritant-induced asthma. Since then, the American College of Chest Physicians has defined RADS as follows (47):

- A documented absence of preceding respiratory complaints
- Onset of symptoms after a single exposure incident or accident
- Exposure to a gas, smoke, fume, or vapor with irritant properties present in high concentrations
- Onset of symptoms within 24 hours after the exposure and persistence of symptoms for at least 3 months
- Symptoms simulating asthma
- Evidence of airflow obstruction on pulmonary function tests and presence of bronchial hyperresponsiveness
- Absence of other pulmonary disease

Evidence from case reports, human studies, and animal toxicologic studies indicates that low-level chronic exposure to respiratory irritants, including volatile organic solvents, can result in acquired bronchial hyperresponsiveness or hyperreactive airways (48). Experimental studies and case reports provide evidence that temporary increases in airway hyperresponsiveness occur after low-level irritant exposure and that persistent asthma can occur after episodes of higher-level irritant exposure. However, the results of epidemiologic studies are conflicting. Whereas population-based epidemiologic studies suggest that occupational solvent exposure can be associated with respiratory symptoms, impaired pulmonary function, and respiratory diseases, many of these studies have suffered from the lack of appropriate controls, which limits their applicability (5,35).

Most consistent information on the respiratory effects of solvents comes from acute high-dose exposures or from acute and chronic exposures to selected solvents. However, individuals exposed to low-level solvent vapors report higher rates of airway irritation, chest tightness, cough, and respiratory symptoms. One study performed on healthy adults in a chamber showed that toluene at a concentration of 100 ppm caused irritation of the eyes and nose but had no effect on pulmonary function (49).

Alkylbenzenes are irritants of the respiratory tract (50). In a controlled exposure study of a mixture of 22 common organic solvents, mucous membrane irritation was shown to occur in the upper airway in healthy subjects at total airborne concentrations of 5 mg per cubic meter (51). Further chamber studies investigated the effects of low-level solvent mixtures on FEV_1 and showed a decline in FEV_1 among subjects who had preexisting bronchial hyperreactivity at concentrations of 25 mg per cubic meter but found no influence on the FEV_1 at concentrations of 2.5 mg per cubic meter (48). Airborne concentrations of 25 mg per cubic meter can commonly be found in the occupational and work environments. Case studies and controlled human studies thus support the conclusion that volatile organic compounds at low-level exposure concentrations can act as bronchial irritants in the work or home environment.

A recent study suggests that long-term solvent exposure may be a cause of sleep apnea (52). Digital oximetry performed on solvent-exposed printers with neurobehavioral complaints who were also nonsmokers showed a significant occurrence of nocturnal oxygen desaturation as compared to unexposed controls. Airborne solvent concentrations did not violate TLVs (52). The clinical significance of this effect remains unknown.

Volatile organic solvents as a group are sensory irritants. The sensory irritation effects of alkylbenzenes, halogenated benzenes, and halogenated alkylbenzenes have been evaluated by investigating the reflexively induced decrease in respiratory rate in mice. It was found that the potencies of alkylbenzenes increase with increasing length of the alkyl chain (53). Studies have shown that exposure to a mixture equal to a total airborne load of 25 mg per cubic meter produces neutrophil influx into the nasal passages, indicating inflammation. The studies showed a statistically significant increase in inflammatory cells immediately after a 4-hour exposure to the volatile organic chemicals and 18 hours after the exposure (54). This 25-mg-per-cubic-meter total volatile organic chemical concentration is considered to be low level and representative of what is found in new homes, office buildings, and spaces with poor indoor air quality. These levels are below OSHA PELs of any one individual chemical found.

Solvents previously were not thought to be able to cause asthma or to act as pulmonary sensitizers. However, a variety of respiratory diseases caused by solvent exposures have been described in the medical literature. Reported postexposure respiratory outcomes have included both restrictive and obstructive processes, including asthma (50). Volatile organic solvents all have the potential to produce mucous membrane irritation. Chemical substances that are reactive and bind to tissues covalently cause irritation. Also, relatively nonreactive substances that bind to tissues physically and reversibly can cause irritation. Nonreactive-type volatile organic compounds predominate in low concentrations in many indoor contaminant situations (55).

Irritation reflects a stimulation of mucous membrane tissues, particularly in the upper airways. The nerves in the airways that mediate irritation also mediate mechanically and thermally induced irritation symptoms and sensations. An important

property is that of temporal summation, whereby the longer a stimulus lasts, the longer will be the sensation of irritation.

Xylenes are an excellent example of an irritating volatile organic chemical. They also produce effects on the CNS and local irritating effects on the eye, nose, and throat (56). In one case report in a small community hospital, 15 people were affected 1 hour after 1 L of liquid xylene was discarded down a laboratory sink. Symptoms reported included headache, nausea, dizziness, and vomiting in addition to eye, nose, and throat irritation (57). Also, neurobehavioral symptoms were reported.

Evidence in case reports, clinical series, and animal toxicologic studies indicate that low levels of volatile organic solvent mixtures can produce upper airway and lower airway irritation and airway hyperreactivity or asthma. Adequate evidence exists that an inflammatory process in the airway wall is the underlying pathophysiologic mechanism of bronchial hyperresponsiveness and asthma. Medical evidence has accumulated that adequately demonstrates that reactive airways or asthma symptoms can be initiated by a low- or moderate-level exposure to an irritant substance (58). Generally, the clinical presentation is that of a patient who has no preceding respiratory complaints or asthma signs or symptoms (but in whom asymptomatic bronchial hyperresponsiveness or a preexisting bronchial hyperresponsiveness may be resident) who develops reactive airways or asthma for the first time after experiencing an irritant exposure that may last only a few minutes or hours, several days, or weeks (58). The irritant is generally in a vapor form but can take the form of particulates or fumes. The exposure levels causing these asthmalike symptoms need not be massive but can be moderate or low level. Respiratory symptoms can develop abruptly or evolve slowly over days or weeks. Initially, upper respiratory symptoms predominate, with eye, nose, and throat irritation and laryngeal symptoms. The individual may develop what seems to be an increased sensitivity to many and varied nonspecific irritants while removed from the exposure source (58). These manifestations have been termed *bronchial irritability* or *bronchial hyperresponsiveness* and include symptoms of coughing, choking, wheezing, and chest tightness occurring after many and varied nonspecific low-level irritant exposures (58).

In one study that examined in a workplace the effects of volatile organic compounds on pulmonary function tests, 42 patients with a history of industrial exposure to organic solvents and pulmonary symptomatology were investigated. Pulmonary function tests were performed, followed by methacholine challenge. Forty-two percent of the patients had significantly abnormal methacholine stimulation tests, whereas only 10% to 15% of these patients had abnormal initial screening spirometry (59). These data show that exposure to volatile organic solvents is associated with bronchial hyperreactivity that is not commonly detected by initial screening spirometry, and so methacholine challenge testing is required in individuals with unexplained respiratory symptomatology and a history of exposure to volatile organic solvents (59). Also, such mucosal irritation can disrupt vocal cord mechanisms (60).

A recent case series reported symptoms of respiratory irritation, breathing difficulties, headache, and nausea among a group of individuals exposed to a collective total volatile organic solvent load (61). In this study, the airborne concentrations of the solvents were well below OSHA PELs. The employee whose problems appeared most clearly to be related to the solvent exposure in the building was a 50-year-old woman who was experiencing persistent hoarseness and episodic shortness of breath and in whom new-onset asthma and new-onset vocal cord dysfunction (based on video laryngoscopy) were diagnosed. This woman was unable to reenter the building without exacerbation of her symptoms. She improved after months of asthma therapy and treatment aimed at vocal cord dysfunction and eventually returned to work.

Another study examined the effect of 32 different volatile organic solvents detected in the air of a printing shop, all of which were present in concentrations lower than regulatory standards. Workers exhibited signs and symptoms of eye, nose, throat, and airway irritation as well as neurobehavioral symptoms (62).

DERMAL ABSORPTION AND TOXICITY

Dermal absorption of alkylbenzenes is a potential route of toxicity. Dermal absorption of a solvent is related to such variables as concentration of the solvent; duration of exposure; the condition, thickness, and vascularity of the skin; and the surface area exposed (63,64). Injury, burn, or rashes will increase solvent absorption. Another important variable that dictates absorption of volatile organic chemicals is the hydration status of the skin. The more hydrated the skin is, as from perspiration or immersion in water, the more chemical absorption is facilitated across the dermal barrier. In addition, increased skin temperature will enhance skin absorption, owing to increased blood flow through the skin.

Absorption variabilities depend also on the anatomic location. The palms of the hands and soles of the feet, for instance, present a dermal barrier to absorption as compared to other parts of the body such as the scalp, neck, or abdomen and scrotal area. Studies have shown that combinations of solvents or multiple solvents in aqueous media have a greater chance of being more readily absorbed than does a pure solvent (59).

Dermal absorption can represent a significant exposure route for some organic solvents and may represent from 30% to 90% of the total daily intake of organic solvents from aqueous media. The absorption of toluene, styrene, xylene, and ethylbenzene across human skin has been studied (Table 105-3) (63,64).

The absorption of toluene across the skin is slow and, in solution, was found to be proportional to the concentration of toluene that came in contact with the skin (63,65). The dermal absorption rate of liquid toluene was 14 to 23 mg per square centimeter per hour in subjects studied. Ethylbenzene demonstrated similar dermal absorption rates depending on the concentration that came in contact with the skin (64). The dermal absorption of liquid styrene was found to be 9 to 15 mg per square centimeter per hour and was linear to the concentration of styrene. The rate of absorption of liquid xylene ranged from 4 to 10 mg per square centimeter per hour.

BIOLOGICAL EXPOSURE INDICES

Biological exposure indices (BEIs) serve as a reference intended to evaluate potential health hazards of chemicals. They represent the level of a metabolite likely to be found in the urine or

TABLE 105-3. Dermal absorption of aromatic solvents

Solvent	Rate	Reference
Toluene (liquid)	14–23 mg/cm²/h	(63)
Xylene (liquid)	4.5–9.6 mg/cm²/h	(63)
Xylene (liquid, hand)	2 μg/cm²/min	(143)
Styrene (liquid)	9–15 mg/cm²/h	(63)
Styrene (liquid, hand)	0.06 mg/cm²/h	(165)
Aqueous styrene solution	40–180 μg/cm²/h	—
Ethylbenzene (liquid, hand)	22–33 mg/cm²/h	(64)
Aqueous ethylbenzene	118–215 μg/cm²/h	—

TABLE 105-4. Aromatic solvent biological exposure indices

Solvent	Urine	Blood	Time	BEI
Toluene	Hippuric acid		End of shift	2.5 g/g creatinine
		Toluene	End of shift	1 mg/L
Styrene	Mandelic acid		End of shift	800 mg/g creatinine
			Prior to next shift	300 mg/g creatinine
	Phenylglyoxylic acid		End of shift	240 mg/g
			Prior to next shift	100 mg/g
		Styrene	End of shift	0.55 mg/L
			Prior to next shift	0.02 mg/L
Xylene	Methyl hippuric acids		End of shift	1.5 g/g creatinine
Ethylbenzene	Mandelic acid		End of shift at end of work week	1.5 g/g creatinine

BEI, biological exposure index.

blood of a healthy worker exposed to chemicals to the same extent as an inhalational TLV exposure. BEIs do not represent a clear distinction between hazardous and nonhazardous exposures. They are influenced by biological variability of individuals. BEIs apply to 8-hour exposure, 6 days per week, and should not be used to determine the presence of adverse effects or for diagnosing an occupational exposure illness.

In some cases, exposure to aromatic organic solvents can be verified by detection of metabolic products in urine or blood (Table 105-4). Coexposure to ethanol or other solvents can decrease the urinary metabolite excretion and increase the blood levels of solvents. Thus, these factors must be considered in biological monitoring interpretation. Physical activity also influences excretion of metabolites by increasing vapor absorption.

TOLUENE

Toluene is an alkylbenzene derived from crude oil and coal tar during petroleum refining. It is formed by attaching one methyl group to benzene (see Fig. 105-1). Toluene is a common component of gasoline, adhesives, paints, inks, and solvents.

Physiochemical Properties

Toluene (methylbenzene) has a molecular formula of $C_6H_5CH_3$ and a molecular weight of 92.15 D. It has a sweet odor and is flammable. The boiling point of toluene is 110.6°C, and its vapor pressure is 22 mm Hg at 20°C. It autoignites at 480°C. Toluene's odor threshold in air is 8 ppm (Table 105-5).

TABLE 105-5. Physiochemical properties of toluene

Synonyms	Methylbenzene, phenylmethane
Molecular formula	$C_6H_5CH_3$
Molecular weight	92.15 D
Physical state	Colorless liquid
Boiling point	110.6°C
Density (20°C)	0.8669 g/L
Odor	Sweet
Odor threshold	
In air	8 ppm
In water	0.04–1.00 ppm
Vapor pressure (25°C)	28.4 mm Hg
Autoignition	480°C
Conversion factor	1 ppm = 3.75 mg/m^3
Explosive limits	
Lower limit	1.3%
Upper limit	7%

Sources, Production, and Uses

Approximately 10% to 11% of the toluene produced in the United States is isolated as toluene, with the remaining 90% being used to formulate gasoline (66). Nonisolated toluene is employed in a mixture with benzene and xylene (BTX) and is added to gasoline to improve octane rating. Isolated toluene is used in solvents, cleaning agents, paints, adhesives, inks, and other commercial chemical products. Toluene also finds use as a starter chemical for the synthesis of such other organic chemicals as urethanes, polyurethane foams, inks, and trinitrotoluene.

Toluene is regulated by the Resource Conservation and Recovery Act as a hazardous waste. Industrial wastes that contain solvents may not be disposed of on land if the extract of this waste contains more than 0.33 mg per L of toluene (66). Also, wastewater containing greater than 1.12 mg per L of toluene may not be land disposed (40 *CFR* 268.41).

Human exposure to toluene occurs from inhalation during occupational use, airborne levels in the home, inhalational abuse of paints containing toluene, and from other sources of environmental release. Toluene is a common indoor air contaminant that averages approximately 30 μg per cubic meter of air (66).

The largest exposure source of toluene is in the production and use of gasoline, which contains 5% to 7% toluene by weight. Large amounts of toluene are introduced into the environment yearly through the use of gasoline and through its production and petroleum refinement processes.

Other environmental sources of toluene are the disposal of solvents in home wastewater, industrial discharges, land disposal of solvents, petroleum wastes, and tobacco smoking. Toluene can volatilize from solvent mixtures, paints, and other products used in the home and occupational settings. Ambient air concentrations of toluene vary in their ranges depending on location (Table 105-6). The main source of toluene in the atmosphere is the use of gasoline.

The presence of toluene in water supplies is generally less than 3 μg per L (66). Toluene commonly contaminates both water and soil in the vicinity of waste sites or chemical and industrial sources that use or produce toluene. Concentrations in the water of such sites range between 7 and 20 μg per L, and concentrations in soil may approximate 70 μg per kg (66). Toluene released into water rapidly volatilizes into the air.

Environmental Fate and Transport

Toluene tends to vaporize into the atmosphere from surface water or soil. After toluene is released into soil, volatilization of more than 90% of the toluene released usually occurs within 24 hours, depending on the environmental circumstances (e.g., tem-

TABLE 105-6. Median toluene levels in ambient air

Air sampled	No. of samples	Daily mean (ppb)	Concentration ($\mu g/m^3$)
Remote	225	0.049	0.18
Rural	248	0.35	1.3
Suburban	958	0.195	0.731
Urban	2,519	2.883	10.81
Indoor	101	8.4	31.5
Workplace	80	0.865	3.24

From ref. 66, with permisison.

perature and humidity) and the type of soil (67). Toluene is soluble in water and can be transported from soil by water runoff, depending on the soil's organic content, as toluene has a higher affinity for soil with an excess of organic matter and is more easily released from soils that have low organic matter content.

Toluene can bioaccumulate in aquatic organisms owing to its lipophilic properties. However, an organism's metabolism limits toluene's ability to bioaccumulate. The highest toluene levels are found in organisms that have a limited ability to metabolize (e.g., crabs) (66). Biodegradation is rapid in both the soil and the atmosphere. Atmospheric toluene is degraded to cresol and benzaldehyde. The primary degradation process in the atmosphere is a reaction with hydroxyl radicals. The atmospheric half-life of toluene is approximately 13 hours (68).

Owing to the miscibility of toluene with water, the rate of aqueous biodegradation is somewhat slower than atmospheric biodegradation. Biodegradation in water occurs mainly through the action of microorganisms; toluene's half-life in this setting ranges between 13 and 54 days. The presence of sulfate enhances aqueous toluene biodegradation (66). Soil biodegradation of toluene by bacteria is mainly by *Pseudomonas* and *Achromobacter* species in two phases: The first phase degrades to benzoic acid, whereas the second phase cleaves the aromatic ring to produce Krebs cycle intermediates.

Exposure Sources

Human exposure to toluene occurs mainly from inhalation. Calculations show that given an average concentration of toluene of 32 μg per m^3 in the indoor air of homes and an inhalation rate of air at 20 m^3 per day, a person can absorb 320 μg per day if only 50% of the inhaled toluene is absorbed (66). Tobacco smoke contributes 1,000 μg of toluene or more per day to the indoor environment.

The OSHA has set a PEL of 200 ppm as a time-weighted average (TWA) for toluene in the work environment. This PEL was recently increased from 100 ppm after a legal decision by the U.S. Supreme Court.

Toluene concentrations found in the indoor air of houses are attributable to volatilization of toluene from paints, solvents, glues, adhesives, environmental tobacco smoke, and other materials used within the home environment. Tobacco smoke is a significant source of toluene within the home environment, as approximately 80 to 100 μg of toluene is released per smoked cigarette.

The National Academy of Sciences has developed a methodology by which to calculate acceptable concentrations of solvents in drinking water. This methodology was incorporated into the U.S. Environmental Protection Agency's (EPA's) suggested no-adverse-response levels. These levels are the highest concentrations of a chemical that produce no observed adverse effect from chronic dosing in animals or humans. The figures are divided by a safety factor to obtain what is termed an *acceptable daily intake.* To calculate the acceptable concentration of a chemical in water, the acceptable daily intake is divided by the volume of water consumed by the average person, either adult or child. The EPA has reported concentrations of toluene in surface water sources ranging from 1 to 2,000 μg per L (66). The daily intake of toluene from drinking water generally is quite small and would be a negligible source of toluene absorption in most cases. Although drinking water contamination by toluene is generally less than 0.1 μg per L, EPA surveys have found levels exceeding 0.1 μg per L. Assuming the ingestion of 2 L of water per day, water intake would contribute a total daily dose of 0.3 to 0.5 μg of toluene (66).

Exposures to toluene also could occur near waste sites or from contaminated water or soil at hazardous-waste sites. Calculating the human exposure to toluene secondary to such waste sites depends on the pathways of migration into air, water, and soil and the human intake of these materials. In situations such as this, exposure occurs primarily via the inhalational and dermal absorption routes.

Absorption, Metabolism, and Excretion

In humans, toluene is absorbed from the respiratory tract and GI tract and through the skin. Owing to the lipophilic nature of this compound, the concentration in lipid tissues can be very high. The metabolism of toluene is depicted in Figure 105-2. Toluene's metabolic products are cresol (less than 1%) and the intermediate metabolite, benzaldehyde. Benzaldehyde then is metabolized to benzoic acid, which is conjugated with glycine to form hippuric acid (69–73). In humans, up to 75% of inhaled toluene is metabolized to hippuric acid and excreted in the urine within 12 hours

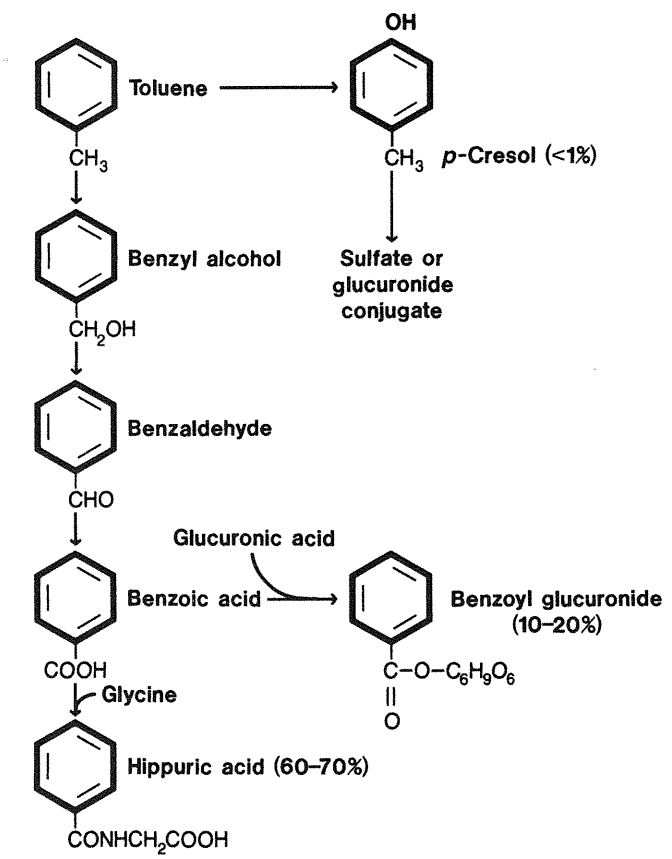


Figure 105-2. Metabolism of toluene in humans.

TABLE 105-7. Toluene health effects

Acute	Brainstem atrophy
CNS depression	Optic neuropathy
Coma	Decreased visual acuity
Agitation	Severe cognitive impairment
Delirium	Oculomotor abnormalities
Euphoria	Corticospinal tract dysfunction
Chronic	Deafness
Permanent CNS impairment	Hyposmia
Tremors	CNS demyelination
Ataxia	Neurobehavioral abnormalities
Cerebral atrophy	Renal tubular acidosis
Cerebellar atrophy	

CNS, central nervous system.

of exposure. The remainder of the toluene is excreted unchanged, with a small percentage being excreted as a sulfate or glucuronide of cresol. The metabolism and excretion of toluene are rapid, occurring within 12 hours of exposure. The half-life of toluene in adipose tissue of humans has ranged from 0.5 to 3 days.

Dermal absorption of toluene ranges from 14 to 23 mg per square centimeter per hour (74) (see Table 105-3). Absorbed toluene is quickly distributed to lipid-containing, highly vascular tissues: the CNS (particularly white matter), bone marrow, liver, kidneys, and nervous tissues.

Clinical Toxicology

Human toxicity from toluene exposure occurs primarily by the inhalational and dermal routes, although ingestion is another absorption route (Table 105-7) (75). Toluene is well absorbed by the lungs (76). It also is absorbed dermally, and rates of absorption have been studied and found to vary from 14 to 23 mg per square centimeter per hour (76). Exposures can be acute, subchronic, or chronic. Humans exposed to concentrations of toluene of between 200 and 800 ppm may experience respiratory and ocular irritation (76,77). Toluene is mildly irritating to the skin and eyes. Chronic contact between toluene and skin can produce irritation in animal models and humans, and direct splashing of the eyes may cause corneal injury. CNS neurotoxicity is the primary concern in toxic inhalational exposure. Toluene's other target organs include the kidneys and mucous membranes.

Controlled exposure effects on volunteers were studied using toluene concentrations of 40, 60, or 100 ppm. The exposed individuals experienced ocular and respiratory irritation along with a perceived deterioration of air quality, enhanced odor, headache, and dizziness at 100 ppm (49). Also at exposures of 100 ppm, psychological measurements indicated decrements in vigilance, visual perception, motor performance, and ability to carry out functions (49).

The toxic health effects of toluene can be acute, subchronic, or chronic, depending on the dose absorbed. Acute effects of inhalational exposure include a euphoric drunken feeling, headache, dizziness, confusion, fatigue, memory difficulties, disturbed equilibrium and balance, disturbed coordination, nausea, vomiting, and if the dose is sufficiently high, loss of consciousness. Inhalational solvent abuse in particular has led to permanent neurologic sequelae and CNS lesions that have been described on CT and MRI.

Chronic exposure to low toluene concentrations is associated with fatigue, headache, dizziness, shortness of breath, cough, throat irritation, nausea, and other constitutional symptoms. Disturbance of vestibuloocular responses has been demonstrated in subjects exposed to concentrations of toluene ranging from 103 to 140 ppm for more than 2 hours while doing light work (78). Color vision has also been shown to be impaired by occupational exposure to toluene (79).

Because of the accumulation of toluene in the CNS's anatomic areas, symptoms can last hours beyond an exposure. Such impairments may be cognitive or involve coordination, motor control, intention tremor, and gait disturbances. Common features in chronic toluene sniffers include euphoria, hallucinations, coma, ataxia, convulsions, cognitive impairment, and diplopia (80).

NEUROTOXICITY

Acute inhalational exposure to high concentrations of toluene vapor causes CNS depression, syncope, euphoria, delusions, acute excitation, and dizziness. Chronic exposure to high toluene vapor concentrations can result in permanent neuropsychological and CNS damage. Severe and persistent neurotoxicity can be a result of chronic toluene inhalation and chronic toluene abuse. Optic neuropathy, hearing loss, cerebellar ataxia, and cognitive dysfunction have all been described. Neuroimaging studies show that CNS white matter changes due to toluene toxicity appear to be irreversible.

Ataxia, tremors, visual impairment, diffuse cerebral atrophy, cerebellar atrophy, and brainstem atrophy occurred after intentional inhalational toluene abuse (81). Decreased vision and ataxia have been described in individuals chronically inhaling toluene-containing solvents (82). Optic neuropathy is manifest as decreased visual acuity but normal pupillary reactions along with associated cerebellar signs. Improvement in vision has occurred after discontinuation of toluene exposure. Rosenberg et al. (81) reported neurotoxicity in chronic toluene abusers that was characterized by severe cognitive impairment, cerebellar ataxia, corticospinal tract dysfunction, oculomotor abnormalities, tremor, deafness, and hyposmia. MRI of the CNS in toluene vapor abusers has demonstrated multifocal CNS involvement and diffuse CNS demyelination (83). The clinical presentation of these individuals included neurobehavioral, cerebellar, brainstem, and pyramidal tract abnormalities. Autopsy findings in those who have died from toluene inhalation revealed diffuse myelin pallor in the deep white matter of the cerebral hemispheres and the cerebellum. In these autopsies, diffuse demyelination of the subcortical white matter and axonopathy of the peripheral and central nervous systems were demonstrated (81).

A strong correlation exists between the concentrations of toluene in alveolar air and concentrations in the blood, so that inhalational exposure to toluene can result in rapid transfer across the alveolar capillary membrane and into the blood. In humans, toluene is distributed between plasma and red cells at a 1 to 1 ratio (84). The penetration of the red cell by toluene allows more of this compound to be transported to target organ sites, including the CNS. Toluene has a predilection to concentrate in lipid tissues. Autoradiographic studies in animals demonstrate that after inhalation of toluene, high levels are found in adipose tissue, bone marrow, nerves, spinal cord, brain white matter, and kidneys, and radioactivity was observed at lower levels in the blood, kidney, and liver (85).

The systemic and anatomic distribution of toluene, particularly in the CNS, has been studied (86). In rats, labeled toluene was detected in all brain regions and in the blood and liver. Maximum concentrations were obtained 10 minutes after inhalation, the greatest concentration being found in the medulla and pons, followed (in descending order) by the midbrain, cerebellum, thalamus, frontal cortex, hippocampus, caudate, and hypothal-

amus (86). The medulla, pons, and midbrain had the highest concentration of toluene.

In the human brain, toluene has a greater affinity for the lipid-rich areas of the white matter (e.g., brainstem) than for the gray matter. In autopsies, the hippocampus and cerebellum had lower brain-to-blood toluene ratios than did the spinal cord, midbrain, medulla oblongata, and pons (87).

Toluene concentrations in individual brain regions are eliminated in an exponential manner, such that almost no toluene remains detectable at the end of 4 hours. Toluene appears to have an affinity for the brainstem regions, medulla, and pons region owing to their high lipid content and regional blood flow differences. Of interest, toluene metabolites have not been detected in the brain (81,82,84–87). Such results correlated to clinical studies indicate that low-level exposure that results in neurologic symptoms such as dizziness, incoordination, and other CNS effects does so because of the rapid toluene buildup in the specific anatomic CNS regions of the brain, with levels reaching their maximum within 10 minutes after inhalational exposure.

Other neurologic findings that have been permanent or, in some cases, partially reversible in inhalational toluene abusers include cerebellar ataxia, intention tremor, ocular dysmetria, pyramidal tract dysfunction, and cognitive impairment. The anatomic regional distributions of toluene help to explain these clinical manifestations.

Organ concentrations of toluene in the case of a human who abused the compound by inhaling it have been described (Table 105-8) (87). The mean ratios of the brain region–to–blood toluene concentration were highest in the brainstem region in areas such as the pons and medulla oblongata. These were followed by the midbrain, thalamus, caudate, putamen, hypothalamus, and cerebellum. The lowest ranges were in the hippocampus and cerebral cortex. Because white matter is enriched with myelin and, therefore, contains more lipid than does gray matter, more toluene concentrates in white matter rather than gray matter. Cerebral cortex and hippocampal areas, which are composed of gray matter, demonstrate the lowest concentrations of toluene (87). Thus toluene, once it passes the blood–brain barrier, is distributed according to the lipid content in the CNS anatomic regions. In other human autopsy cases, toluene concentrations have been documented in the various tissues and fluids (Table 105-9) (88).

TABLE 105-8. Regional brain distribution of toluene in a human autopsy case

Sample	Toluene concentration (μg/g)	Ratio (brain–blood)
Brain region		
Cerebral cortex	8.18	1.76
Hippocampus	6.86	1.47
Caudate-putamen	8.71	1.87
Thalamus	8.93	1.91
Hypothalamus	9.51	2.04
Corpus callosum	12.40	2.66
Midbrain	10.78	2.31
Pons	10.20	2.18
Medulla oblongata	10.42	2.23
Cerebellum	7.03	1.51
Cervical spinal cord	11.00	2.35
Blood		
Femoral vein	4.61	—
Thoracic cavity	4.67	—

Adapted from ref. 87, with permission.

TABLE 105-9. Toluene concentrations in various fluids and tissues of human death case

Samples	Concentration (μg/g)
Blood	27.6
Heart	62.6
Liver	433.5
Lung	27.4
Kidney	23.0
Brain	85.3
Spleen	30.0
Pancreas	88.2
Skeletal muscle	27.2
Cerebrospinal fluid	11.1
Fat	12.2
Small gastric content	38.2
Stomach content	1,071.5
Urine	2.1

Adapted from ref. 88, with permission.

NEUROIMAGING AND ELECTROPHYSIOLOGIC PATHOLOGY OF TOLUENE TOXICITY

MRI in toluene abusers reveals diffuse cerebellar atrophy, cerebral atrophy, and atrophy of the brainstem, with decreased differentiation between gray and white matter and increased periventricular white matter signal intensity on T2-weighted images (34). Toluene abuse also is associated with cerebellar and cerebral atrophy on CT scans. Other radiologic findings on CT scans include widening of the cerebellar and cerebral sulci and basal cisterns and enlargement of the ventricular system. Neurologic lesions on MRI and CT scanning correlate with impairments on psychological tests in toluene abusers.

Neuropathologic changes correlated with MRI or CT scanning in toluene abuse patients include diffuse cerebral demyelination, diffuse cerebellar demyelination, demyelination of subcortical white matter, degeneration and gliosis of ascending and descending long fiber tracts and nerves of the corpus callosum, and atrophy of the cerebrum, cerebellum, and corpus callosum (89). Necropsy showed myelin pallor in deep periventricular white matter, with axonal and neuronal loss combined with demyelination. EEG abnormalities are reported in some cases (90).

Individuals exposed to long-term low concentrations of toluene as compared to controls showed abnormal VEPs (90). Toluene exposure was determined in this study by measuring toluene in blood and hippuric acid and *o*-cresol levels in urine.

CARDIOTOXICITY

Cardiotoxicity (e.g., cardiac dysrhythmias), as is seen in toxic exposures to such other solvents as the chlorinated solvents, is not commonly observed in human exposures to toluene. However, animal studies involving chronic dosing of toluene intraperitoneally and subcutaneously have demonstrated atrial fibrillation and ventricular ectopy (75).

HEMATOTOXICITY

A decreased leukocyte count has been observed in dogs exposed acutely to 700 ppm of toluene (75). This and other hematologic effects (e.g., thrombocytopenia) have been observed in other animal studies after the animals' exposure to toluene. A report

from the National Toxicology Program in 1989 stated that exposure to toluene concentrations of up to 1,200 ppm for 2 years or less had no hematopoietic systemic effects on mice or rats (75). Human occupational exposure studies also have not demonstrated hematologic effects (77). Previous investigations linking toluene to hematotoxicity failed to account for coexposures to other solvents.

HEPATOTOXICITY

In most studies of human exposure to toluene, hepatic damage has not been observed (77,91,92). Likewise, in animal studies conducted by the National Toxicology Program, toluene was not observed to be hepatotoxic; the studies were conducted in mice over a 2-year period, and the mice were exposed to toluene doses of 1,200 ppm (75). Nonetheless, some clinical reports of acute reversible liver damage after inhalational abuse of toluene have been published (75,92–94). Other cases of single-dose, massive exposure have resulted in coma but no demonstrated liver injury.

Occupational studies of exposed workers have failed to demonstrate a consistent pattern of liver injury or hepatic enzyme elevation (75,91–93). In most occupational studies, other solvents are involved and present a confounding factor.

Occupational studies of painters exposed to a wide variety of solvents, including toluene, have demonstrated elevation of hepatic enzymes (94). Biopsies revealed liver histopathologic findings of steatosis and enlarged portal tracts with fibrosis and necrosis (94).

RENAL TOXICITY

Toluene can cause nephrotoxicity in two forms: acute renal failure after massive ingestions and distal renal tubular acidosis (95–100). Clinical reports state that excess proteinuria, abnormal liver function test results, interstitial nephritis, and glomerulonephritis have also been related to toluene exposure (95–100). Nephrotoxic effects that have been documented in chronic toluene abusers include hematuria, proteinuria, and type 1 renal tubular acidosis (92,93,101–105). In contrast, animal studies have been conflicting: In some studies, renal toxicity has been observed, whereas in others, it has not.

Workers exposed to more than 100 ppm of toluene for 6.5 hours demonstrated no significant increase in urinary excretion of β_2-microglobulin, a sensitive indicator of distal renal tubular damage. Other workers exposed to toluene levels of 80 to 107 ppm as well as other solvents did not exhibit increased urinary excretion of β_2-microglobulin (105).

Chronic toluene inhalational abuse can result in a normal anion gap metabolic acidosis with hypokalemia, hypophosphatemia, and hyperchloremia. This type of acidosis was first described in association with glue sniffing and is termed *type I renal tubular acidosis* (102). Renal tubular acidosis is a derangement in the capacity of distal renal tubules to maintain a hydrogen ion gradient and usually is reversible within a few days once exposure to toluene ceases, although reversal of this disorder may require several weeks (103). Treatment ranges from observation to administration of sodium bicarbonate and potassium, depending on the severity of the acidemia and electrolyte loss (103). Patients with metabolic acidosis after toluene inhalational abuse have also exhibited associated hypokalemic muscular weakness and paralysis with neuropsychiatric manifestations (106).

TERATOGENICITY, MUTAGENICITY, AND REPRODUCTIVE EFFECTS

Animal studies have shown developmental effects secondary to toluene exposure (107–109). Developmental effects have been demonstrated also in pregnant women exposed occupationally to solvents, including toluene, and in pregnant women as a result of solvent abuse (109). However, determining whether the toluene was actually causative is difficult, because these women were exposed to multiple solvents as well as to drugs and medications.

Children with microcephaly, minor craniofacial and limb anomalies, CNS defects, attention disorders, developmental delay, learning disorders, and language deficits were born to mothers who abused toluene by inhalation during pregnancy (108,109). Whether these congenital defects and conditions are secondary to toluene abuse alone remains unclear. However, exposure to organic solvents in general may have some embryotoxic effect. The term *fetal solvent syndrome* has been applied to such conditions.

Reproductive effects associated with toluene exposure have included an increased spontaneous abortion rate among women exposed to an average of 88 ppm of toluene (110), changes in gonadotropic hormone levels, and decreased levels of luteinizing hormone, follicle-stimulating hormone, and testosterone after exposures to increasing levels of toluene (from 8 to 111 ppm) (111,112).

Toluene has an adverse effect on the developing fetus in animal studies. Neonates born to women who were chronic inhalational abusers of toluene have exhibited renal tubular acidosis at birth that resolved within a few days (94,113). Increased risks of CNS defects, anomalies, and developmental delays are suggested in some studies, but these studies have been retrospective and were compromised by multiple confounding factors (113,114).

Studies examining the incidence of sister chromatid exchange frequencies and chromosomal aberrations in workers occupationally exposed to toluene have been reported (115–117). These studies indicated an increased frequency of sister chromatid exchanges. However, the relevance of these findings is unclear, as workers in the studies experienced multiple other chemical exposures.

CARCINOGENICITY

Toluene is considered to be noncarcinogenic, as no human epidemiologic studies indicate that toluene exposure increases the risk of carcinogenesis. Animal studies also have not demonstrated carcinogenic effects of toluene. Retrospective mortality studies of humans occupationally exposed to toluene have included exposures to other chemicals.

IMMUNOTOXICITY

No human data exist to indicate that toluene is an immunotoxicant. Animal studies involving mice exposed to toluene in drinking water for 28 days (105 ng of toluene per kg of body weight per day) showed a decrease in thymus weights, mixed lymphocyte culture response, antibody plaque-forming cell response, mitogen-stimulated lymphocyte proliferation, and presence of interleukin-2 (118).

Biological Monitoring

Hippuric acid is used as a biological marker for occupational exposure to toluene (see Table 105-4). Minor toluene metabolites are *o*-cresol, *p*-cresol, and phenol. The minor metabolites are conjugated with either sulfate or glucuronic acid and are excreted in the urine (70–73).

Individual variations with respect to metabolism of toluene and the correlation of occupational exposure to toluene and urinary excretion of hippuric acid and cresol metabolites can occur, especially if there is coexposure to other solvents or ethanol (72,119). Ethnic variations in toluene metabolism also are seen (119). Owing to this variability of metabolism among individuals, the biological monitoring of hippuric acid and other metabolite excretions is merely a qualitative indication of exposure and not a quantitative indication of toluene toxicity.

Studies performed in occupational settings have indicated that both hippuric acid and *o*-cresol excretion are related to the environmental concentration of toluene and workers' exposure, if excretion is corrected for creatinine and urine specific gravity (77). The correlation coefficient was stronger for hippuric acid (0.88 and 0.84) than it was for *o*-cresol (0.63 to 0.62) (69).

The urinary excretion of hippuric acid is a reliable biological indicator of low-level toluene exposure. At exposures below the TLVs of toluene, urinary concentrations of hippuric acid and *o*-cresol may increase (69).

The presence of ethanol will decrease the metabolic clearance of toluene (120–123). Propranolol and cimetidine do not affect toluene metabolism (121). Blood concentrations of toluene have been shown to increase in exposed workers during shifts and to correlate with the air concentrations (124).

The combination of ethanol and toluene increases the hepatotoxicity of toluene, owing to inhibition of metabolism. Human studies indicate that even low ethanol blood levels inhibit toluene metabolism (70). Even a single alcoholic drink produces this metabolic inhibitory effect. Hippuric acid excretion was decreased by an ethanol dose of 0.32 g per kg (69). A source of error in the biological monitoring of toluene can be introduced by dermal absorption (125).

Toluene interferes with benzene metabolism and its hematopoietic toxicity (126). The toxicity of benzene depends on its metabolism to myelotoxic and clastogenic by-products. Benzene is metabolized to phenol first, by P-450 monooxygenases in the liver, and then to hydroquinone. Final benzene toxic metabolites are benzoquinones and semiquinone radicals, which are produced by bone marrow myeloperoxidase action on hydroquinone (127). Both the P-450 enzyme system and myeloperoxidase enzymes are inhibited by toluene to the degree that coexposure to both benzene and toluene inhibits benzene metabolism and immunotoxicity in mice. Evidence of this protective effect has also been found in humans (74,83,128,129).

Regulatory Aspects

The OSHA PEL TWA is 200 ppm, with a 15-minute ceiling of 300 ppm. The ACGIH, in 1996, recommended a TLV of 50 ppm with no designated short-term exposure limit (STEL). The ACGIH 15-minute ceiling limit is 150 ppm. The recommended BEI in urine for hippuric acid is 2.5 g per gram of creatinine at a work shift's end. The National Institute of Occupational Safety and Health (NIOSH) recommends a TLV of 100 ppm, with a 10-minute ceiling of 200 ppm. The toluene vapor concentration that is considered immediately dangerous to life and health (IDLH) is 2,000 ppm. The EPA recommends a maximum concentration level in water of 1 mg per L.

XYLENE

Xylene (dimethylbenzene) is a commonly used aromatic solvent with three isomeric forms: *ortho-*, *meta-*, and *para*-xylene (see Fig. 105-1). Xylenes are one of the highest-volume chemicals produced and used by industry. A mixture of all three isomers is termed *xylol*. Xylene is a sweet, clear liquid solvent, the vapors of which can be very irritating to eyes, nose, throat, skin, and mucous membranes (130). It is flammable, volatile, and soluble in alcohol and organic liquids but relatively insoluble in water.

Physiochemical Properties

Physiochemical properties of xylene are listed in Table 105-10. Each isomeric form of xylene is a colorless liquid that is highly volatile.

TABLE 105-10. Physiochemical properties of xylenes

	o-Xylene	*m*-Xylene	*p*-Xylene
Physical state (20°C; 101.3 kPa)	Colorless liquid	Colorless liquid	Colorless liquid
Boiling point (°C; 101.3 kPa)	144.4	139.1	138.3
Melting point (°C; 101.3 kPa)	–25.2	–47.9	13.3
Relative density (25°/4°C)	0.876	0.860	0.857
Vapor pressure (kPa at 20°C)	0.66	0.79	0.86
Flash point (°C) (closed cup)	30	25	25
Saturation % in air (101.3 kPa)	1.03 (32%)	1.03 (28%)	1.03 (27%)
Explosion limits (vol% in air)	1.0–6.0	1.1–7.0	1.1–9.0
Autoignition temp (°C)	465	525	525
Octanol–water partition coefficient (log P)	3.12	3.2	3.15
Solubility in water (mg/L)	142	146	185

Adapted from World Health Organization. *Xylenes.* Environmental health criteria 190. Geneva: World Health Organization, 1997.

Sources, Production, and Uses

Mixed xylene isomers (*m-*, *o-*, and *p*-isomers) are widely used as solvents. The physical and chemical properties of each isomeric form are similar (127). All mixed commercial xylene produced by catalytic processing of petroleum is a combination of 20% *o*-xylene, 44% *m*-xylene, and 20% *p*-xylene, and also contains 15% ethylbenzene (130). Xylene is produced also from coal tar, which yields an isomer mixture of 45% to 70% *m*-xylene, 23% *p*-xylene, 1% to 15% *o*-xylene, and 6% to 10% ethylbenzene (130).

Commercial xylene often is contaminated with other organic compounds such as ethylbenzene, toluene, benzene, trimethylbenzene, phenol, thiophene, and pyridine. The volumes of these contaminants are very minor, making up less than a fraction of 1% (130).

Xylene is used in paints, inks, dyes, varnishes, and glues. Both xylene and xylol are used by histology technicians for tissue preparation. Xylene, toluene, and benzene (BTX) are blended into gasolines. Xylene is used as a solvent vehicle for pesticides and in manufacturing epoxy resins, coatings, fabrics, perfumes, and insect repellents. Seventy percent of xylene is used to produce ethylbenzene (130).

The xylene isomers are used as chemical intermediates in the synthesis of other compounds. *m*-Xylene is used to produce isophthalic acid, *m*-toluic acid, and isophthalonitrile (130). Isophthalic acid is used to make polyesters. *o*-Xylene is used to manufacture phthalic anhydride for plasticizers, terephthalic acid for polyesters, isophthalic acid, vitamins, and pharmaceuticals (130). *p*-Xylene is a chemical intermediate for synthesizing dimethyl terephthalate and terephthalic acid for polyesters and for vitamins and pharmaceuticals. *p*-Xylene and *o*-xylene are also components of insecticides (130).

Environmental Fate and Transport

Owing to low vapor pressures, volatilization is the main process that governs xylene transport and environmental behavior. Xylenes readily volatilize from ground and water sources into the atmosphere, where they are quickly transformed by photooxidation via hydroxy radicals (130). Xylenes are relatively stable to oxidation and hydrolysis in water. Biodegradation of xylenes occurs in surface soils but is a slow process (130).

Xylene can occasionallybe detected degassing from landfill disposal hazardous-waste sites. Average air levels detected have

ranged from 0.86 mg per cubic meter for *o*-xylene (0.20 ppm) to 3.6 mg per cubic meter for *m*-xylene (0.83 ppm) and 1.2 mg per cubic meter for *p*-xylene (0.28 ppm) (130).

Xylenes are introduced into groundwater by releases of fuel oil, gasoline, and industrial spills; leaking storage tanks; and leaching from disposal waste sites. Xylene isomers have been detected in leachate at concentrations of 10 to 4,400 µg per L for hazardous-waste sites and from 3.7 to 38.0 µg per L for domestic landfills (130).

Xylene readily partitions from water and soil into the atmosphere, with a half-life of 5.6 hours at a depth of 1 m (130). Spills into soil result in both volatilization and soil leaching. As the organic content of the soil increases, the residence time of xylene increases (130). Xylene tends to adsorb to highly organic soil. In subsurface soils with a low organic content, xylene will be more quickly transported to groundwater. Xylene moves through unsaturated soil faster than through polar substances and water.

Exposure Sources

Because xylenes are ubiquitous in the environment, exposure to xylene can occur both in and out of an occupational setting. Xylenes are detected in the atmosphere, soils, surface waters, sediments, rain, drinking water, aquatic organisms, human blood, urine, and expired alveolar air (130).

Xylenes do not occur naturally in the environment. Their presence is due to releases from industrial sources, automobile exhaust, petroleum refining, commercial uses, and general solvent volatilization, spills, and waste disposal. Individuals are exposed to xylene while pumping gas. This compound can enter the soil and groundwater after releases of gasoline, fuel oil, and other xylene-containing solvent mixtures. Surface releases result in rapid volatilization into the atmosphere.

Tobacco smoke contains xylene, which can be detected in the blood of smokers (131). The breath level of xylene is twofold higher in smokers as compared to nonsmokers (132). Indoor environmental levels of xylene in 350 residences studied were 3 parts per billion (ppb) for *m*-xylene and *p*-xylene and 1 ppb for *o*-xylene (133). Blood xylene levels in nonoccupationally exposed individuals ranged from 0.074 to 0.78 ppb for *m*-xylene and *p*-xylene and 0.044 to 0.30 ppb for *o*-xylene (134).

Absorption, Metabolism, and Excretion

Xylene is absorbed via the inhalational, dermal, and GI routes. Inhalation of xylene vapors is a common occupational exposure route, and urinary metabolites increase as the level of respiratory exposure increases. Approximately 60% of inhaled xylene is absorbed (135).

The kinetics of *m*-xylene have been studied in humans (135–138). Physical exercise results in increased absorption of solvent vapors through increased rate of ventilation. One study examined 18 healthy male volunteers and carried out controlled studies of *m*-xylene vapor exposure (138). The results showed that the concentration of xylene in blood samples increased with physical activity. Alveolar air concentrations of xylene were increased 40% over baseline after exposure to 30 ppm during exercise (139).

Xylene is a GI irritant and a mucous membrane irritant. GI absorption occurs after ingestion, and urinary metabolites can be detected.

Dermal xylene absorption is low as compared to respiratory tract absorption (see Table 105-3). Liquid xylene penetrates hand skin at a rate of 2 µg per square centimeter per minute (140). Other studies demonstrate dermal absorption rates varying from 4.5 to 9.6 mg per square centimeter per hour (63). Dermal absorption of xylene increased with prolonged immersion in liquid and is increased by a factor of three if the dermis is damaged (140,141).

Xylene is very soluble in blood and lipid-containing tissue. Thus, its distribution depends on blood flow to organs and tissue lipid content. Organs with high blood perfusion will receive more xylene. Adipose tissue has a slow continuous xylene uptake lasting beyond termination of an exposure. Thus, the potential exists for adipose tissue accumulation of xylene in chronic exposure (142). During exercise, xylene appears to be shunted to subcutaneous tissues and adipose stores.

Xylene CNS levels approximate those of blood, the concentration in the brain being approximately 40% of that of arterial blood (135). Studies in animals indicate that the rate of rise of blood xylene is correlated with CNS rise of xylene and acute symptoms. Accumulation of xylene in the brains of rats is both time and concentration dependent.

The biotransformation of xylene through side chain oxidation and aromatic oxidation results in metabolites of methylbenzyl alcohols, methylbenzaldehyde, and methylbenzoic acids (toluic acids) (143). Methylbenzoic acids are conjugated with glycine to form methyl hippuric acids, the main urinary metabolites of xylene. A minor (1% to 4%) metabolic pathway of xylene metabolism is aromatic ring hydroxylation, which forms xylenol (143).

In summary, less than 5% of xylene is excreted unchanged in exhaled air, approximately 95% is excreted as methyl hippuric acid metabolites, and 1% to 4% is excreted as xylenol metabolites (Fig. 105-3).

Aromatic compounds are metabolized via the P-450 mixed-function microsomal enzyme system in the endoplasmic reticulum of the liver. The coingestion of ethanol will inhibit the metabolism of xylene (136). Ethanol inhibits oxidation of both the aromatic ring and the alkyl side chain, probably through a direct inhibitory effect on microsomal oxidation by ethanol. Xylene blood concentrations increase up to twofold after ethanol ingestion, indicating inhibition of metabolism (136). Liver necrosis and steatosis have been reported after xylene exposure (137).

Despite the fact that ethanol decreases xylene metabolism by 50%, the urinary excretion of 2,4-xylenol, a minor xylene metabolite, was not decreased by ethanol (136). The ingestion of moderate doses of ethanol has increased blood xylene concentrations twofold. Coingestion of ethanol and xylene also results in a decrease in methyl hippuric acid excretion in the urine. The ratio of 2,4-xylenol to methyl hippuric acid was significantly increased with the combination of alcohol ingestion and xylene exposure.

Xylene clearance is mainly renal, and 36% is excreted by the end of a work period in which exposure occurs, whereas 70% to 80% of xylene metabolites are excreted within 24 hours of exposure termination (143). Coexposure to other solvents affects xylene metabolism (144). Exposure to both methyl ethyl ketone and xylene results in approximately a 50% increase in blood xylene concentrations. Also, urinary excretion of methyl hippuric acid decreases, indicating competition for enzyme metabolism (144). Coexposure to trichloroethylene, ethylbenzene, and toluene also inhibits xylene metabolism (145). Increased use of the minor aromatic ring hydroxylation pathway occurs when other solvents compete with P-450 enzyme pathway metabolism.

Clinical Toxicology

Exposure to xylene is common as it is a constituent of paints and glues and is used as a general solvent in many processes and products. Owing to its high vapor pressure, most exposures to xylene and its isomers are by inhalation.

Death has been reported in an individual who was exposed to paint solvents containing primarily xylene, the estimated atmospheric concentrations being 10,000 ppm (146). Autopsy of

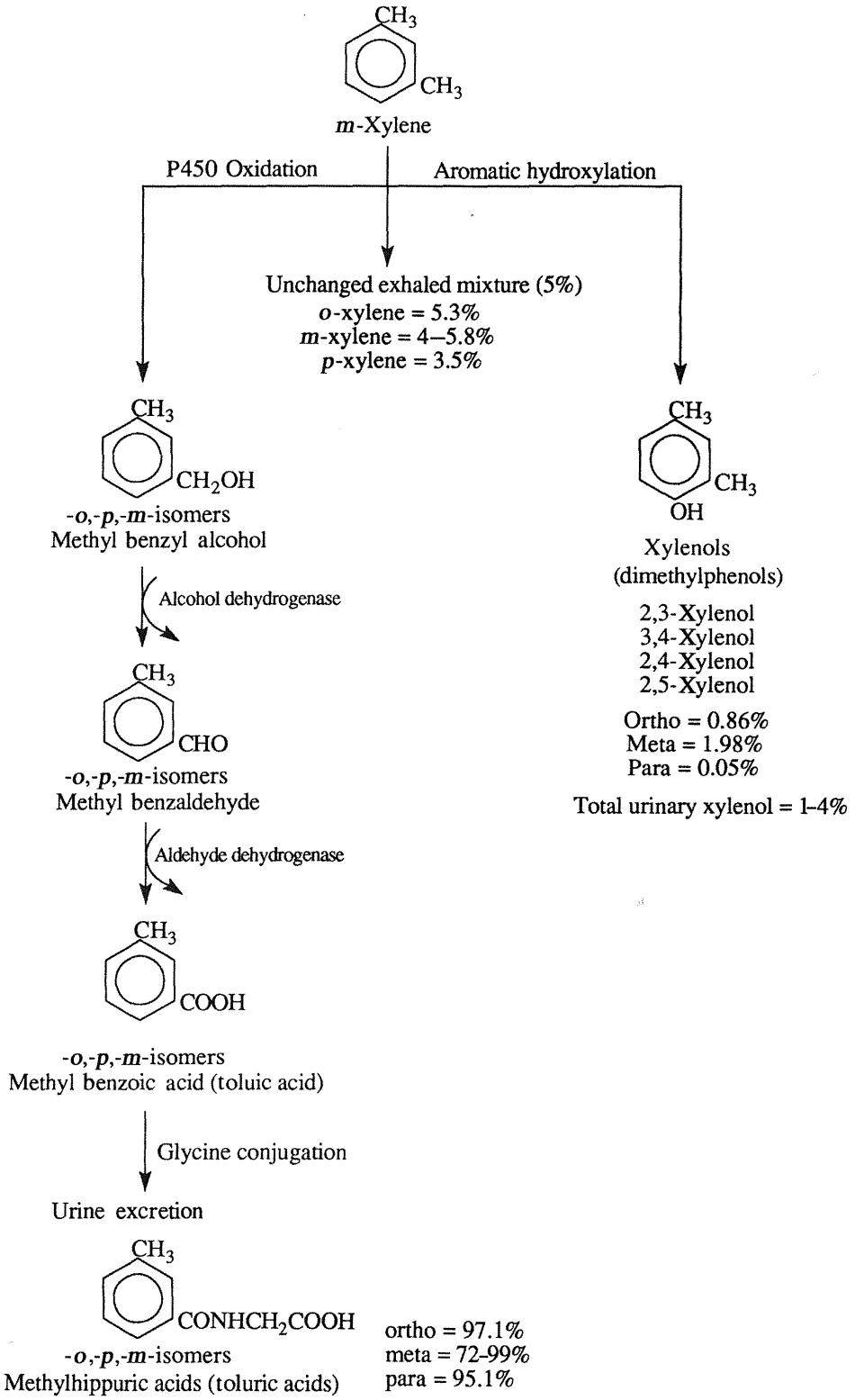


Figure 105-3. Xylene metabolism.

this individual demonstrated severe pulmonary congestion with hemorrhage and pulmonary edema. Data in animal models suggest that *p*-xylene might be more toxic than the other xylene isomers.

OCULAR AND PULMONARY SYSTEM EFFECTS

Nose and throat irritation from xylene has been reported at 200 ppm for 3 to 5 minutes and 100 ppm for 1 to 7.5 hours per day for 5 days (130). Chronic occupational exposure to unspecified or unknown concentrations of xylene vapors has been associated with difficulty breathing and impaired pulmonary function (147,148). Nose and throat irritation has been reported with increased prevalence by workers who are exposed chronically to xylene vapors at a geometric mean TWA concentration of 14 ppm (56).

A wide body of literature exists showing upper airway, throat, eyes, and nose irritation caused by acute inhalational exposure to xylene at varying concentrations (56,130). Such adverse respiratory effects are noted also in animal models after

acute and intermediate inhalational exposure to xylene. These effects include decreased respiration, increased labor of breathing, respiratory irritation, pulmonary edema, pulmonary hemorrhage, and pulmonary inflammation (130).

NEUROTOXICITY

Case reports and studies provide evidence that acute and chronic inhalational exposure to xylene or solvent mixtures containing xylene are associated with neurotoxicity and neurobehavioral changes. Neurologic signs and symptoms have included headache, nausea, dizziness, difficulty concentrating, impaired memory, slurred speech, ataxia, fatigue, agitation, confusion, tremors, and noise sensitivity (57,130,149,150). In many of these case reports, exposures have included multiple solvents in which xylene was involved as the main component; hence, confounding factors compromise such studies.

In one study in which the xylene exposure was defined, 175 workers in a Chinese factory who were exposed for an average of 7 years reported neurobehavioral symptoms consisting of headache, anxiety, forgetfulness, nightmares, decreased concentration, and decreased grasp (149). These employees were exposed to mixed xylene airborne concentrations on an 8-hour TWA of 21 ppm, in which xylene accounted for more than 70% of the total exposure and *m*-xylene specifically for 50% of the exposure. Animal studies lend support to the theory that mixed xylene isomers are neurotoxic after inhalation (130).

The odor threshold of xylenes depends on the isomer. On average, the odor threshold appears to be approximately 1.0 ppm. *m*-Xylene has an airborne odor threshold of 3.7 ppm, *o*-xylene 0.17 ppm, and *p*-xylene 0.47 ppm.

Xylene vapors have a sweet odor that, in conjunction with irritation of the airways and respiratory tract, will cause most individuals to note the presence of the compound at high concentrations and to avoid it. Individuals who may be tolerant of the odor or who remain in the area of airborne xylene may develop headaches, nausea, vomiting, fatigue, dizziness, irritability, insomnia, a drunken feeling, impaired memory, loss of coordination, and unsteady gait, in addition to upper airway and ocular irritation (149–151).

Neurobehavioral symptoms may be the first indication of low-level xylene intoxication. The CNS effects of xylene are excitatory and occur mainly during the absorptive phase of xylene exposure, whereas a depressive effect occurs during the elimination phase of xylene exposure (151).

Subjects exposed to 690 ppm of mixed xylene for 15 minutes experience dizziness, but this same symptom was reported by only one of six persons exposed to 460 ppm (152). Other studies showed no impairment in performance tests in subjects exposed to 299 ppm for 70 minutes (153) or at 396 ppm in men for 30 minutes (154,155). Some studies report prolongation of reaction times in exposure to xylene at 100 ppm for 4 hours (155).

Increased theta waves over occipital regions are seen in EEG results in subjects exposed to xylene peaks of 200 ppm for 4 hours (150). Other researchers report that xylene exposure for 6 hours for 6 to 9 days with levels fluctuating between 64 and 400 ppm produced impairment in balance and reaction time (156,157). Peripheral neuropathy has been associated with xylene exposure, but no biological or chemical mechanism has been established, although it is thought that xylene interrupts fast axonal transport (158).

Biological Monitoring

Assays of blood and alveolar air can detect xylene, and its metabolites can be detected in urine. Blood levels of xylene can be affected by coexposure to other solvents. Coexposure to toluene, trichloroethylene, ethylbenzene, methyl ethyl ketone, or alcohol is known to increase xylene blood concentrations by competing for metabolic enzymes (144,145,159). Aspirin decreases methyl hippuric acid urinary excretion (160).

The BEI for xylene reflects an 8-hour TWA exposure period resulting in a urinary concentration of 1.5 g per gram of creatinine of methyl hippuric acid. This level should not be exceeded if daily xylene exposure levels are no higher than 100 ppm.

Exercise increases xylene absorption from the lungs and methyl hippuric acid urinary excretion. One study showed that physical exercise increased methyl hippuric acid urinary excretion by 24% (138).

Regulatory Aspects

Regulations limiting xylene exposure are as follows: The OSHA PEL (TWA) is 100 ppm, as is the ACGIH TLV-TWA. The ACGIH's 15-minute STEL is 150 ppm. According to the NIOSH, the IDLH level is 900 ppm. Odor thresholds of 1 ppm in air and 0.017 mg per L of water have been described. The EPA recommends a maximum concentration level in water of 10 mg per L.

STYRENE

The natural source of styrene (cinnamene, vinyl benzene, ethenyl benzene, phenylethene, phenylethylene) is the sap of the styracaceous tree.

Physiochemical Properties

Styrene, a colorless to yellow oily liquid, is flammable and has a flash point between 73° and 141°F. Styrene has a molecular formula of C_8H_8 and a molecular weight of 104.1 D (see Fig. 105-1). It is a 99% pure mixture of styrene monomers having an odor threshold in air of 0.32 ppm and an odor threshold in water of 0.011 mL per L. Its vapor density is 3.6 (as compared to that of air, which is 1.0). At low concentrations, its odor is sweet, but at higher concentrations, the odor becomes disagreeable (161). Table 105-11 lists physiochemical properties of styrene.

Styrene is synthesized from benzene by alkylation with ethylene, which forms ethylbenzene, which is followed by dehydrogenation to form xylene. Styrene monomers are reactive at high temperatures and pressures and undergo polymerization on exposure to light and air. They also undergo oxidation and formation of peroxides. Polymerization of styrene monomers can occur if styrene is heated to 150°F or higher temperatures. Metal salts and acids can also cause polymerization to occur. Styrene reacts violently with chlorosulfonic and sulfuric acids (161).

Sources, Production, and Uses

Common uses of styrene are in the production of polystyrene plastics, styrene-butadiene rubber, and acrylonitrile-butadiene-styrene polymers and resins. Styrene is also used to produce styrene-butadiene latex protective coatings and in the formation of polyesters and copolymer resins.

Environmental Fate and Transport

Most styrene that is released to the environment volatilizes into the atmosphere. However, styrene can also contaminate soil and groundwater. Investigations report that between 87% and 95% of styrene in landfill soil is converted to carbon dioxide within 16 weeks (162). Various fungi and bacteria grow on styrene, thus indicating that it is biodegradable.

TABLE 105-11. Physiochemical properties of styrene

Molecular weight	104.14 D
Molecular formula	C_8H_8
Autoignition temperature	490°
Explosiveness range	1.1–6.1% by volume in air
Solubility	Slight in water Miscible in alcohol, ether, methanol, acetone, carbon disulfide
Specific gravity	0.9045 (25/25°C)
Boiling point	145.2°C
Vapor pressure (mm Hg)	
–1.6°C	1
20°C	4.5
25°C	6.1
33°C	10
66°C	50
Volume in saturated air	8,026 ppm
Conversion factors	1 ppm = 0.00426 mg/dL 1 mg/L of vapor = 234.7 ppm
Partition coefficients	
Water/air	4.38
Blood/air	32
Oil/blood	130
Oil/air	4,160

Studies show that styrene rapidly volatilizes from shallow bodies of water, with 50% being lost in 1 to 3 hours (162). However, only 26% of styrene is volatilized from a soil depth of 1.5 cm within 31 days. Within 30 hours of a release into soil, 9% of styrene is adsorbed to minerals and organic soil (162).

Styrene is rapidly biodegraded by microorganisms in aerobic environments, but this rate of biodegradation slows when styrene concentrations are low in water or aquifers and in low-pH environments (162). Aerobic microorganisms in soil convert styrene to 2-hydroxyphenylacetic acid and styrene oxide, which then are biodegraded further. The mineralization of styrene in soil is proportional to its concentration.

Exposure Sources

Styrene exposure can occur during the manufacturing of plastics, polymers, and styrene-butadiene rubber and during its use as a solvent and in resins. Exposure to styrene also can occur in boat building and manufacturing of fiberglass-reinforced plastics. Use of a variety of styrene-containing products (e.g., paints, waxes, polishes, adhesives, cleaners, putty, varnishes) can result in exposure. In addition, environmental tobacco smoke and automobile exhaust contain styrene.

Styrene is detectable in air at vapor concentrations of 0.32 ppm. Aldehydes and peroxides can form from styrene when it is exposed to air, increasing its disagreeable odor. The vapors of styrene are very irritating.

Styrene is detected in the blood of nonoccupationally exposed individuals, indicating the potential environmental exposure sources (163). Styrene can also migrate from polystyrene plastics into packaged foods, which represent a possible source of styrene ingestion (164).

Absorption, Metabolism, and Excretion

Styrene is absorbed via respiratory, dermal, and GI routes. Systemic absorption of styrene via respiration is increased with increasing physical activity. Uptake is five to six times greater during heavy physical labor (165). From 60% to 70% of inhaled styrene is absorbed in humans, and 85% of this inhaled styrene is eliminated in the urine as mandelic acid and phenylglyoxylic acid metabolites (see later). Only 1% to 3% of styrene is exhaled unchanged. Styrene has dose-dependent kinetics (166). A BEI is based on the urinary excretion of mandelic acid (see Table 105-4).

Dermal absorption of styrene is considered to be minimal. However, skin absorption does occur and rates have been determined for both vapor and liquid (see Table 105-3) (63,167). Percutaneous absorption of styrene is increased if skin is injured.

Absorbed styrene is first metabolized by hepatic cytochrome P-450 enzymes to styrene-7,8-oxide, which is considered to be the main toxic metabolite, even more toxic than styrene. Styrene and styrene oxide are metabolized further by the liver as well as by the kidney, intestines, lungs, and skin. Styrene oxide is metabolized to phenylethylene glycol by microsomal epoxide hydrolase and, subsequently, to its two major metabolites, mandelic acid (85%) and phenyl glyoxylic acid (10%) (166,168,169). Up to 90% of absorbed styrene is excreted as urinary metabolites (Fig. 105-4) (170,171). A minor metabolic pathway involving phenylethylene glycol and mandelic acid is metabolism to benzoic acid, which then is conjugated with glycine to form hippuric acid.

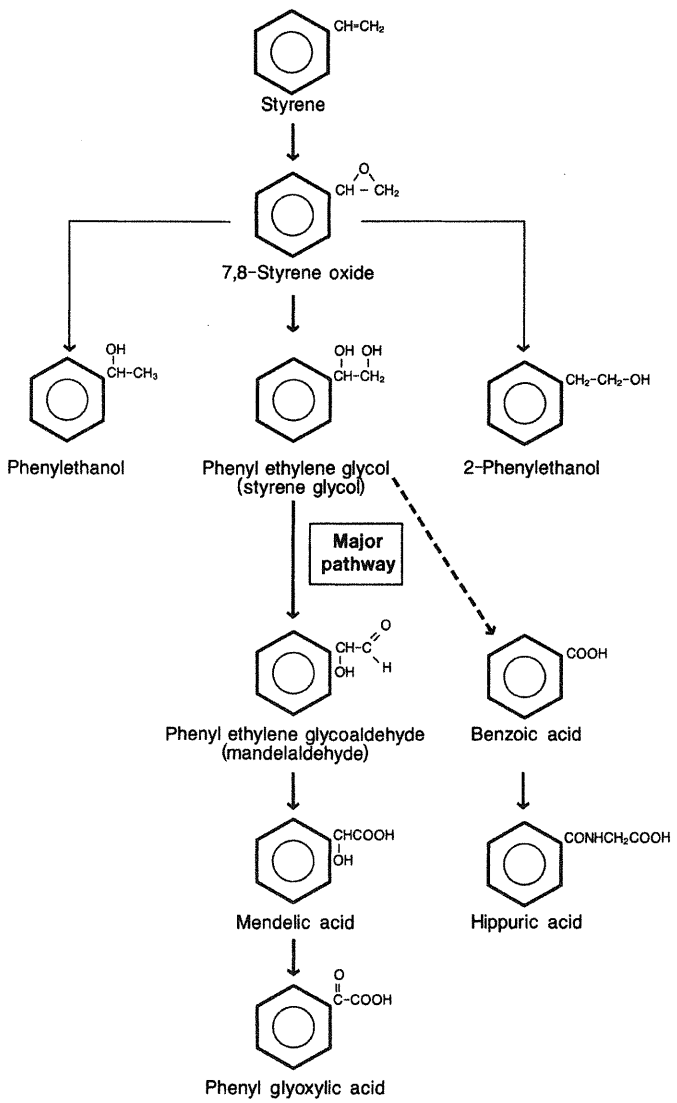


Figure 105-4. Metabolism of styrene.

Styrene dermal absorption has been studied using the urinary excretion of mandelic acid as a marker. The rate of absorption of liquid styrene across the dermal barrier was 9 to 15 mg per square centimeter per hour. The rate of aqueous solution absorption was 40 to 180 μm per square centimeter per hour, and the absorption from solution was linear with the concentration (63,64,165,167).

The metabolism of styrene is inhibited by ethanol as well as other solvents. Styrene metabolism is suppressed by coexposure to toluene. Acute alcohol ingestion inhibits P-450 enzymatic metabolism of styrene. Chronic ethanol ingestion will increase metabolism via induction of hepatic microsomal oxidizing enzymes, with increased formation of styrene-7,8-oxide (172). Coexposure to trichloroethylene or to toluene will inhibit styrene metabolism (173). Animal models indicate that ethanol and styrene coexposure decreases levels of brain glutathione (174). The major metabolite of styrene found in the urine is mandelic acid. The excretion of mandelic acid in the urine appears to be linearly related to exposure to styrene up to 150 ppm (175). Investigations have shown that the summation of mandelic acid and phenylglyoxylic acid in the urine correlates with total exposure to styrene.

Other minor metabolites of styrene metabolism are 4-vinyl phenol, phenylethylene glycol, phenylethanol, and hippuric acid (175). Styrene toxicity is believed to be related to styrene-7,8-oxide, which is four times as toxic as styrene (176). Styrene-7,8-oxide is formed in the brain and liver and can react with macromolecules and DNA to disrupt cellular physiology (177). The oxide is an alkylating agent and reacts with deoxyguanosine in DNA, forming 7-alkylguanine. Styrene-7,8-oxide also reacts with deoxycytidine, forming *N*-3-alkylcytosine. The conjugation of styrene-7,8-oxide with glutathione is a protective metabolic action. Decreased brain levels of glutathione can thus contribute to tissue injury (178).

Styrene is eliminated in a biphasic pattern, with first rapid elimination from blood followed by slower elimination from adipose tissue. Studies of exposure to styrene concentrations of 3 to 20 ppm show a second-phase half-life of 3 to 5 days (179).

Clinical Toxicology

Styrene exposure causes both acute and chronic toxicity (Table 105-12). Styrene is a central and peripheral neurotoxin and an irritant to the respiratory tract and to mucous membranes (166,168,169). Styrene-7,8-oxide is believed to be the major toxic metabolite that produces injury.

Acute toxic effects of styrene include mucous membrane irritation, respiratory irritation, headache, dizziness, decreased attention span, nausea, vomiting, impaired memory, and fatigue. Styrene is a neurotoxin with adverse effects on both the central and peripheral nervous systems.

Exposure of volunteers to styrene vapors of up to 375 ppm for up to 1 hour resulted in eye irritation and nasal irritation along with burning of the skin and face (180). In the same study, vapors of 50 to 115 ppm caused subjects to report strong odors but produced no signs and symptoms. At the 375-ppm level, some subjects reported difficulties in manual dexterity and balance and feelings of inebriation, especially after 60 minutes of exposure. Individuals exposed to much higher concentrations of styrene reported ocular irritation, throat irritation, drowsiness, vertigo, CNS depression, and unsteadiness of gait (169).

The health effects of styrene are dose related. Mild complaints consist of mucous membrane irritation, headache, nausea, vertigo, and fatigue. Workers exposed to between 4 and 165 ppm also expressed more complaints of depression, tinnitus, ocular irritation, and dizziness (181).

Chronic exposure to styrene has produced neurobehavioral symptoms with complaints of attention deficit, memory problems, fatigue, paresthesia, and muscle weaknesses (166,182). Workers exposed to styrene vapors of 3 to 251 ppm for a median duration of 7 years were compared with unexposed controls. Neurologic examination showed no evidence of peripheral neuropathy or encephalopathy in these exposed individuals as compared to controls. Neurobehavioral assessments involving intelligence, reaction time, short-term memory, and personality also demonstrated no differences between exposed and unexposed control subjects (183).

Other workers exposed chronically to styrene in industry have reported symptoms of excessive tiredness, difficulty concentrating, nausea, and memory disturbances. Styrene concentrations in their environment ranged from less than 20 to more than 150 ppm (182).

NEUROTOXIC MANIFESTATIONS

Neurophysiologic studies indicate that styrene is a central and peripheral neurotoxin. Abnormal EEG reaction times and NCVs have been found in workers who were exposed to styrene and reported neurobehavioral and neurologic symptoms. Reviews of EEG studies in populations of workers confirmed that exposure to high levels of styrene produce quantitative EEG changes. However, many of these workers were exposed to multiple

TABLE 105-12. Styrene neurotoxicity

Target organ or assessment tool	Symptoms	Concentration	Reference
Neurobehavioral effects	Depression, headache, difficulty concentrating, memory deficit, fatigue	20–150 ppm	182
		4–165 ppm	181
		30 ppm	195
		>50 ppm	196
Electroencephalographic effects	Dose-related abnormal changes, including excessive diffuse theta-wave activity, bilateral spike and wave discharge, local slow waves	5–125 ppm	184–186
Peripheral neuropathy	Prolonged motor and sensory conduction velocities	5–125 ppm	186
		3–63 ppm	186,188
	32 workers with urinary mandelic acid >250 mg/L	<40 ppm	189–191
		<50 ppm	
Evoked potentials effects	Somatosensory evoked potential abnormalities after 5–22 years' exposure	140–570 mg/m^3	187
Autonomic nervous system	Electrocardiographic R-R disturbance	22 ppm	188
	Urinary mandelic acid <420 mg/g creatinine		
Balance equilibrium	Balance and sway disturbance on posturography after 6–15 years' exposure		192,193
Hearing	Abnormal response to audiometric tests		179
Color vision	Impairment of blue-yellow and red-green vision		194

other solvents, which introduces confounding factors (184). Nonetheless, dose-dependent EEG changes—diffuse and localized theta waves, increased beta activity in central and rostral hemispheres, and increased fast- and slow-wave activity—have been reported (185,186).

Evoked potential studies comparing styrene-exposed workers to unexposed controls indicated that SEPs, especially peripheral and cortical SEPs, showed prolonged latencies (187).

Neurophysiologic studies involving motor conduction velocities and NCVs in styrene-exposed workers exhibited significantly slower sensory conduction velocities and NCVs. These workers were exposed to a range of 3 to 63 ppm, and mandelic acid and phenylglyoxylic acid metabolites in the urine were monitored. These results suggest that styrene has effects on faster myelinated fibers in the peripheral nervous system (188).

The fact that styrene is a peripheral neurotoxin has been confirmed in nerve conduction studies. However, exposure to less than 100 ppm has not been associated with peripheral neuropathy (183). Other reports have cited increased frequency of peripheral neuropathologic alterations in nerve conduction studies of radial and peroneal nerves in workers exposed to styrene monomers (186,189).

The relationship between styrene exposure and NCVs was investigated in 32 exposed workers and a control group (190). This study demonstrated a dose-response relationship between urinary mandelic acid concentration and ulnar and peroneal motor distal latencies. Those workers with urinary mandelic acid concentrations greater than 250 mg per L had significantly longer latencies than did those whose urinary concentrations did not exceed 250 mg per L. Airborne styrene concentrations were reported to be less than 40 ppm. However, some high concentrations (117 ppm and 94.8 ppm) were noted.

Sensory conduction defects also were found in other workers with chronic styrene exposure, some of whom were exposed to concentrations of less than 50 ppm of styrene (191). As the concentration of styrene increased to between 50 and 100 ppm, the incidence of sensory conduction defects increased. Up to 71% of subjects studied showed defects when styrene concentrations exceeded 100 ppm. Cessation of exposure resulted in improved conduction velocities. Thus, termination of exposure can improve the neuropathologic signs and symptoms of chronically exposed workers.

Styrene adversely affects balance and equilibrium (192,193). Exposed styrene workers (as compared to unexposed controls) were assessed for balance, sway, and changes in hearing. Abnormal findings in speech and cortical response to audiometric tests were noted in 7 of 18 workers (192,193). The exposed group also showed significant balance disturbance on testing. Further studies suggest that styrene interferes with the cerebellar inhibition of the vestibulooculomotor system (169). Other research has revealed impairment of color vision in exposed workers (194). In these subjects, blue-yellow vision was affected, although red-green vision loss has also been reported (194).

As mentioned, neuropsychological abnormalities have been detected in individuals exposed chronically to styrene. Impairment of short-term memory has been noted in individuals exposed to styrene levels of approximately 30 ppm for up to 5 years (195). Other studies have confirmed similar findings in neuropsychological tests involving short-term memory. Neuropsychological tests administered include simple reaction time, choice reaction time, and digit span. The combined urinary metabolites of mandelic acid and phenylglyoxylic acid measured at the end of the work shift were determined to be 575 mg per gram of creatinine (195). When compared to unexposed controls, the exposed individuals showed significant detriments of short-term memory and simple and choice reaction times.

Likewise, workers exposed to airborne styrene concentrations in excess of 50 ppm have demonstrated decrements on neuropsychological tests (including short-term memory tests) as compared to those who were exposed to less than 50 ppm (196).

Other studies have examined neurobehavioral changes in individuals exposed to 12 ppm of styrene. Symptoms included fatigue and memory problems and, among those subjects with higher exposures, headache, irritability, and difficulty in concentrating also were observed. In this study, no differences on neurobehavioral testing were noted between the groups at this airborne concentration (197). It must be emphasized that in *all* studies of neurobehavioral and neuropsychological testing, exposure to multiple solvents can be a confounding factor.

Autonomic nervous system disruption has been demonstrated at airborne styrene concentrations of 22 ppm and mandelic acid urinary concentrations of less than 420 mg per gram of creatinine (188). This disturbance was seen in the R-R electrocardiographic interval ($CV_{R\text{-}R}$), which is a method by which to check autonomic nervous system function in the hypothalamus and brainstem.

MECHANISM OF NEUROTOXICITY

The mechanism by which styrene causes neurotoxicity is unknown, but it is thought that the styrene-7,8-oxide probably plays a role because of its highly reactive alkylating features. Investigators have shown that specific regions of the brain are affected by styrene, with astrogliosis in the sensory motor cortex and hippocampus that persist for months after exposure has been terminated (198). Investigations have shown increased concentrations of glial cell protein markers as an indicator of brain injuries. Exposure of cultured cells to styrene oxide increased concentrations of extracellular calcium and decreased intracellular concentrations of glutathione and adenosine triphosphate (199). Styrene also interferes with the activity of the dopaminergic system and causes a decrease in dopamine levels in the striatum and tuberoinfundibular system of exposed animals at vapor concentrations of 750 ppm (200).

Biological Monitoring

Styrene easily crosses the blood–brain barrier into the CNS and, therefore, blood levels alone will not accurately reflect toxic effects.

The peak urinary excretion of mandelic acid occurs at approximately 4 to 8 hours after styrene exposure. Mandelic acid has a half-life in urine of 7.8 hours after exposure to between 50 and 200 ppm, and phenylglyoxylic acid has a urinary half-life of 8.5 hours (201).

Current ACGIH BEIs for styrene exposure are listed in Table 105-4. The concentration of urinary mandelic acid should not exceed 300 mg per gram of creatinine at the beginning of a work shift or 800 mg per gram of creatinine at the end of a shift. The sum of mandelic acid and phenylglyoxylic acid more accurately reflects exposure and should not exceed 1,000 mg per gram of creatinine at the end of a work shift. Phenylglyoxylic acid also is used as biological marker of exposure, but this acid is unstable unless the urine is frozen immediately; otherwise, the levels will decrease owing to decarboxylation.

Because coexposure to ethanol, toluene, or xylene can result in decreased mandelic acid excretion, detection of stereochemically different enantiomers of styrene metabolites (as opposed to ethylbenzene metabolites) is recommended (202). Mandelic acid produced by styrene metabolism is racemic, composed of *R*- and *S*-enantiomeric forms, whereas mandelic acid produced by ethylbenzene metabolism occurs only in the *R*-enantiomeric form (202).

Styrene metabolism also produces specific mercapturic acids, termed *M1* and *M2*, and correlations have been identified between

the urinary excretion of these mercapturic acids and BEIs (203). Styrene is metabolized by hepatic cytochrome P-450 enzymes to two enantiomeric forms—*R*–styrene oxide and *S*–styrene oxide—which can covalently bind to macromolecules. Styrene oxide metabolism follows two pathways: hydrolysis to styrene glycol or conjugation with glutathione. Glutathione conjugation of styrene oxide enantiomers (*R*- and *S*-) results in urinary excretion of distinctive *N*-acetyl-*S*-C1-phenyl-2-hydroxyethyl-*S*-cysteine (M1) and *N*-acetyl-*S*-C2-phenyl-2-hydroxyethyl-L-cysteine (M2) metabolites, with two diastereoisomer forms: M1-*S*, M1-*R* and M2-*S*, M2-*R* (203).

In an exposure study in which the mean airborne styrene concentration was 112 mg per cubic meter (44 to 228 mg per cubic meter), M1 and M2 mercapturic acid urine concentrations proved to be a reliable parameter of exposure. Workers with a urinary mandelic acid concentration of 200 mg per L excrete a total M1 plus M2 concentration between 0.8 and 2.0 mg per gram of creatinine. Some authors have suggested that the stereochemically selective enantiomers are responsible for the toxic mutagenic potential of styrene (204).

Regulatory Aspects

Regulatory limits for styrene have been established as follows: The OSHA PEL standard for exposure to styrene monomers is 100 ppm, with a ceiling value of 200 ppm (15-minute TWA) and an acceptable exposure of 600 ppm for 5 minutes in any 3-hour period. The ACGIH recommends a TLV-TWA of 50 ppm and a STEL of 100 ppm. The ACGIH TLV-TWA is 50 ppm (215 mg per cubic meter), and the STEL is 100 ppm (425 mg per cubic meter). The NIOSH recommended exposure limit (10-hour TWA) is 50 ppm; the STEL, 100 ppm; and the IDLH, 700 ppm.

In storage, styrene monomer vapors may form polymers. Consequently, the Hazardous Materials Transportation Act designates styrene monomers in quantities of 1,000 pounds or more as a hazardous material for transportation purposes. Any styrene monomer is considered to be a flammable liquid and requires such labeling.

CHLOROBENZENE

The chlorobenzenes are aromatic compounds formed by the addition of between one and six atoms of chlorine directly to the benzene ring. This chlorination process can result in 12 different compounds subdivided as follows: MCB; three isomeric forms each of di-, tri-, and tetrachlorobenzenes; pentachlorobenzene; and hexachlorobenzene (Table 105-13) (205). Substitution of chlorine on the aromatic ring is indicated as follows: 1-monochlorobenzene, 1,2-dichlorobenzene, 1,2,3-trichlorobenzene, 1,2,3,4-tetrachlorobenzene, and 1,2,3,4,5-pentachlorobenzene (see Fig. 105-1).

Physiochemical Properties

With the exception of MCB, 1,2-dichlorobenzene, 1,3-dichlorobenzene, and 1,2,4-trichlorobenzene, which are colorless liquids used as solvents in intermediate chemicals and chemical processes, chlorobenzenes are white, crystalline solids at room temperature. The water solubility of chlorobenzenes decreases with increasing chlorination. The flammability of these compounds is low, and the octanol-water partition coefficients are moderate to high and increase with increasing chlorination. The vapor pressures of these compounds is low to moderate and decreases with increasing chlorination (205).

Commercially used chlorobenzenes are contaminated with a variety of isomers. Pure MCB can contain as much as 0.05% benzene and 0.1% dichlorobenzenes. Technical-grade 1,2-dichlorobenzene can contain up to 19% of other dichlorobenzenes (205).

TABLE 105-13. Chlorobenzene compounds derived by chlorination

Compound	Abbreviated chemical name	Molecular formula
Monochlorobenzene	MCB	C_6H_5Cl
1,2-Dichlorobenzene	1,2,-DCB	$C_6H_4Cl_2$
1,3-Dichlorobenzene	1,3,-DCB	$C_6H_4Cl_2$
1,4-Dichlorobenzene	1,4,-DCB	$C_6H_4Cl_2$
1,2,3-Trichlorobenzene	1,2,3-TCB	$C_6H_3Cl_3$
1,2,4-Trichlorobenzene	1,2,4-TCB	$C_6H_3Cl_3$
1,3,5-Trichlorobenzene	1,3,5-TCB	$C_6H_3Cl_3$
1,2,3,4-Tetrachlorobenzene	1,2,3,4-TeCB	$C_6H_4Cl_4$
1,2,3,5-Tetrachlorobenzene	1,2,3,5-TeCB	$C_6H_4Cl_4$
1,2,4,5-Tetrachlorobenzene	1,2,4,5-TeCB	$C_6H_2Cl_4$
Pentachlorobenzene	PeCB	C_6HCl_5
Hexachlorobenzene	HxCB	C_6H_6Cl

MCB's odor can be described as mild to somewhat sweet and aromatic. It is a colorless, flammable liquid that reacts violently with oxidizers. Vapors can form dangerously explosive mixtures with air, because MCB is highly reactive and its vapors are heavier than air. MCB vapors can travel along floors to ignition sources. The vapor density of MCB is 3.88 (as compared to that of air, which is 1). When heated, toxic combustion products include chlorine gas.

Sources, Production, and Uses

MCB and dichlorobenzenes are produced by direct chlorination of benzene using a Lewis acid catalyst such as ferric chloride (205). Trichlorobenzenes are obtained from the chlorination of dichlorobenzenes, and tetrachlorobenzenes are produced by adding chlorine to trichlorobenzenes. The tetrachlorobenzenes are precursors of pentachlorobenzene. MCB makes up 70% of the world production of all chlorobenzenes (205).

The chlorobenzenes are used as intermediates in the synthesis of pesticides and other chemicals. MCB is used as an intermediate in the manufacture of chloronitrobenzenes, diphenyloxide, DDT, and silicones. It is also a solvent used with methylene diisocyanate; for adhesives; in polishes, waxes, and pharmaceutical products; and with natural rubber.

1,2-Dichlorobenzene is used as a solvent for organic materials, in drain cleaners, in the manufacture of 3,4-dichloroaniline, as a solvent carrier for the production of toluene diisocyanate, and in the manufacture of dyes, fumigants, and insecticides. 1,3-Dichlorobenzene is used as a fumigant and an insecticide. Table 105-14 lists the uses of various other chlorobenzene compounds (205).

Environmental Fate and Transport

Chlorobenzenes as a chemical family can persist in soil for several months, in air for 3.5 days, and in water for 1 day or less. Chlorobenzenes released into water environments will evaporate from water to the atmosphere.

Henry's law constant, the soil sorption constant (K_{oc}), and the octanol-water (K_{ow}) constant predict movement and fate in the environment. The distribution from water to air will decrease with increasing chlorination of the compound. Ninety-six percent of MCB is released to the atmosphere from aquatic environments (206). In other studies, 99% of MCB, 1,2-dichlorobenzene, 1,4-dichlorobenzene, and 1,2,4-trichlorobenzene evaporated from water solutions within 4 hours (205).

TABLE 105-14. Chlorobenzene uses

Compound	Uses
MCB	Intermediate in the manufacture of chloronitrobenzenes, diphenyl oxide, DDT, and silicones; as a process solvent for methylene diisocyanate, adhesives, polishes, waxes, pharmaceutical products, and natural rubber; as a degrading solvent
1,2-DCB	In the manufacture of 3,4-dichloroaniline; as a solvent for a wide range of organic materials and for oxides of nonferrous metals; as a solvent carrier in the production of toluene diisocyanate; in the manufacture of dyes; as a fumigant and insecticide; in degreasing hides and wool; in metal polishes; in industrial odor control; in cleaners for drains
1,3-DCB	As a fumigant and insecticide
1,4,-DCB	As a moth repellent, general insecticide, germicide, space deodorant; in the manufacture of 2,5-dichloroaniline and dyes; as a chemical intermediate; in pharmaceutical products; in agricultural fumigants
1,2,3-TCB	As a chemical intermediate; otherwise, same as those for 1,2,4-TCB
1,2,4-TCB	As an intermediate in the manufacture of herbicides; dye carrier, dielectric fluid; solvent; heat-transfer medium
1,3,5-TCB	Solvent for products melting at high temperatures; coolant in electrical insulators; heat-transfer medium, lubricant, and synthetic transformer oil; termite preparation and insecticide; in dyes
1,2,3,4-TeCB	Component in dielectric fluids; in the synthesis of fungicides
1,2,3,5-TeCB	Not available
1,2,4,5-TeCB	Intermediate for herbicides and defoliants; insecticide; moisture-resistant impregnator; electric insulation; in packing protection
1,2,4,5-TeCB	Formerly in a pesticide used to combat oyster drills; chemical intermediate

Adapted from ref. 205, with permission.

The half-life of chlorobenzenes released into aquatic environments is 100 days, with the majority being released to the atmosphere and the remainder being present in lake outflows and sediments (207). Some studies report that up to 50% of MCB evaporated from sandy soil having a low organic content over a 21-day period and that 50% of 1,4-dichlorobenzene and 1,2,4-trichlorobenzene were degraded or unaccounted for, indicating that they may have leached into groundwater (208).

Because of their chemical structure, the chlorobenzenes are environmentally persistent. Photochemical reactions and microbial degradation are the most likely path for their removal and biotransformation. Soils rich in organic matter and aquatic sediments will adsorb these compounds. 1,2-Dichlorobenzene and 1,2,4-trichlorobenzene are especially persistent in the environment, with half-lives from 1 day in rivers to 10 days in lakes and 100 days in groundwater (209).

Atmospheric chlorobenzenes are degraded by sunlight. They can also be adsorbed onto particulates that can be removed by precipitation.

Dichlorobenzenes, trichlorobenzenes, and pentachlorobenzenes are resistant to microbial degradation in soil and produce chlorophenol degradation by-products. The highly chlorinated chlorobenzenes are not very reactive compounds and disappear slowly from the environment via photolysis, hydrolysis, and oxidative reactions. However, photodegradation occurs slowly.

The half-life of 1,4-dichlorobenzene under artificial sunlight irradiation is estimated to be 115 hours (205). Reductive dechlorination is the photochemical reaction involving chlorobenzenes. The biodegradation of chlorobenzenes has been reported in various studies using soil, sediment, and sewage sludge (205).

Bioaccumulation of chlorobenzenes by aquatic organisms is reflected by the octanol-water partition coefficient. Uptake from water by aquatic organisms increases with increasing chlorination, which increases the chlorobenzenes' lipid solubility. Also, the adsorption of chlorobenzenes onto soil organic matter increases with increasing chlorination. Biomagnification up the food chain has not been studied.

In summary, chlorobenzenes move preferentially from water to the atmosphere but, in waters containing large amounts of organic materials, chlorobenzenes may be retained by the organic material and move into the aquatic environment. The concentration in sediments in aquatic environments is high—at least 1,000 times higher than the concentration found in water. Thus, soils rich in organic matter are major environmental sinks for the chlorobenzenes.

Exposure Sources

Exposure sources of chlorobenzenes are ambient outdoor air with mono-, di-, and trichlorobenzene concentrations ranging from the low microgram-per-cubic-meter range up to 100 μg per cubic meter (205). Concentrations of chlorobenzenes in the indoor air are similar to those in the ambient outdoor air but, occasionally, indoor air concentrations may be found to be higher. Tables 105-15 and 105-16 summarize select indoor and outdoor concentrations of chlorobenzenes.

TABLE 105-15. Chlorobenzenes in indoor air

Compound	Location	Concentration (μg/m³)
MCB	Urban office, United States	1.8–3.2
	Greensboro, NC	Median 0.09
	Baton Rouge–Geismar, LA	Median 2.1
	Houston, TX	Median 5.5
1,2-DCB	Personal air samples	
	Los Angeles, CA, February	0.4
	Los Angeles, CA, May	0.3
	Contra Costa, CA, June	0.6
1,3-DCB	Netherlands, postwar homes	Median <0.6
	Netherlands, <6-year-old homes	Median <0.6
	Rotterdam, Netherlands	Median <0.6
1,4-DCB	Netherlands, postwar homes	Median 2
	Netherlands, <6-year-old homes	Median <0.6
	Rotterdam, Netherlands	Median <0.6
1,3-DCB, 1,4-DCB	Personal air samples	
	Elizabeth/Bayonne, NJ, fall	45
	Elizabeth/Bayonne, NJ, summer	50
	Elizabeth/Bayonne, NJ, winter	71
	Los Angeles, CA, February	18
	Los Angeles, CA, May	12
	Contra Costa, CA, June	5.5
1,2,3-TCB	Netherlands, postwar homes	Median <0.8
	Netherlands, <6-year-old homes	Median <0.8
	Rotterdam, Netherlands	Median <0.8
TeCBs	Love Canal, NY, house basements	0.03–20.0
PeCB	Love Canal, NY, house basements	Trace–0.49

Adapted from ref. 205, with permission.

TABLE 105-16. Chlorobenzenes in outdoor air

Compound	Location	Concentration ($\mu g/m^3$)
MCB	U.S. cities	
	Newark, NJ	0.5
	Elizabeth, NJ	0.4
	Camden, NJ	0.3
1,2-DCB	U.S. cities	
	Los Angeles, CA, February	0.2
	Los Angeles, CA, May	0.8
	Contra Costa, CA, June	0.07
	Elizabeth/Bayonne, NJ	0.17
	Canadian cities	
	Montreal	0.0
	Toronto	0.02
1,3-DCB	Germany; city and environs (Bochum)	3.7
1,4-DCB	Northern Italy, various towns	<5
1,2,4-TCB	U.S. cities	
	Los Angeles, CA	0.05
	Phoenix, AZ	0.02
	Oakland, CA	0.02

Adapted from ref. 205, with permission.

Absorption, Metabolism, and Excretion

Chlorobenzenes are readily absorbed from the GI and respiratory tracts. Chlorobenzenes are distributed into highly perfused tissues and accumulate in lipid tissues. Lipid accumulation is greatest for the more highly chlorinated chlorobenzene compounds.

Chlorobenzenes are metabolized by microsomal oxidation to form arene oxide intermediates and then further to their corresponding chlorophenols, which are excreted in the urine as mercapturic acids after conjugation with glutathione or as glucuronic acid or sulfate conjugates. A small percentage are eliminated unchanged in expired air or feces (205).

MCB is metabolized to an arene oxide and then to phenolic compounds and mercapturic acid. The major MCB urinary metabolites are 4-chlorocatechol and 4–chlorophenol–mercapturic acid. 2-Chlorophenol, 3-chlorophenol, 4-chlorophenol, and 3-chlorocatechol are minor metabolites of MCB. The availability of glutathione and conjugation of the catechol and chlorophenol metabolites play an important role in the production of metabolites of MCB. Saturation of glutathione conjugation is thought to be important in the manifestation of toxic effects of MCB exposure (210).

A minor metabolite of 1,4-dichlorobenzene is 2,5-dichloroquinol. Mercapturic acids and catechols are not formed during metabolism of 1,4-dichlorobenzene in animals (205). Dichlorophenol is detected in the urine of workers exposed to 1,4-dichlorobenzene in amounts ranging from 10 to 230 mL per L (205).

Metabolic products of trichlorobenzenes proceed through arene oxides and form trichlorophenols, with minor metabolites including trichlorocatechols and mercapturic acids. Tetrachlorobenzenes are slowly metabolized to tetrachlorophenols, with arene oxides as metabolic intermediates (205). Mercaptotrichlorophenols and trichlorophenol are metabolites of tetrachlorophenols in animal models. Tetrachlorophenols are primarily metabolized to pentachlorophenol by oxidation or to 2,3,4,5-tetrachlorophenol via the arene oxide intermediate.

Clinical Toxicology

Occupational exposure data are available from case reports and reveal many confounding variables, including dose, exposure duration, and coincident exposures to other solvents. Case reports of MCB occupational exposure cite headaches, lethargy, and ocular and upper respiratory tract irritation as common symptoms after chronic exposure.

Reports of worker exposure to 1,2,-dichlorobenzene have offered conflicting accounts of hematologic disorders, including anemia and leukemias, after long-term inhalational exposure. However, a cross-sectional epidemiologic study of workers exposed to 1,2-dichlorobenzene demonstrated no evidence of hematologic effects at mean levels of 90 mg per cubic meter (215 ppm) (205). Chromosomal aberrations consisting of single and double breaks in peripheral leukocytes were reported in laboratory workers exposed to 1,2-dichlorobenzene vapors as compared to unexposed laboratory personnel (211). Of all the white blood cells analyzed, approximately 9% of the exposed cells contained aberrations, as compared with only 2% of the control group's cells. However, a confounding factor was the lack of a determination of exposure concentrations in air.

CNS depression, excitation, and seizures are possible after ingestion of liquid chlorobenzenes. Inhalation of high concentrations of MCB has produced CNS depression, seizures, muscular twitching, cyanosis, and cardiac arrhythmias. The compound is toxic by inhalation and by absorption through skin. MCB is also irritating to mucous membranes and the respiratory tract. Repeated exposures to the skin can produce dermatitis.

Irritation of the eyes and mucous membranes in humans occurs at approximately 200 ppm, at which level the odor threshold has been greatly exceeded. Hence, the odor threshold and irritative phenomena are insufficient to provide a protective warning about exposure.

Regulatory Aspects

The OSHA PEL as a TWA for MCB is 75 ppm. The NIOSH IDLH value is 2,400 ppm. The ACGIH has recommended a TLV-TWA for chlorobenzene of 10 ppm and has proposed that this compound be designated an A3 (animal) carcinogen.

ETHYLBENZENE

Ethylbenzene, a colorless, liquid solvent, is an irritant of the skin, mucous membranes, and eyes. At high concentrations, it can produce CNS depression in both humans and animals. The OSHA PEL for ethylbenzene is 100 ppm.

Physiochemical Properties

Ethylbenzene (phenylethane) has a molecular formula of $C_6H_5(C_2H_5)$ (see Fig. 105-1). Its physiochemical properties are summarized in Table 105-17. It is a highly volatile liquid aromatic solvent with a vapor pressure of 7 mm Hg (20°C). Its odor threshold is approximately 20 to 100 ppb. Ethylbenzene is a fire and explosion hazard; it reacts violently with oxidizing materials.

Sources, Production, and Uses

Ethylbenzene is found as a natural component of petroleum oil and refined petroleum products. It is formulated also by the alkylation of benzene with ethylene. Gasoline can contain up to 20% ethylbenzene. Ethylbenzene's high vapor pressure allows it to volatilize quickly into the atmosphere from release sources.

Ethylbenzene is a by-product of incomplete combustion of natural materials and is found in tobacco smoke and by-products of vehicle exhaust.

TABLE 105-17. Physiochemical properties of ethylbenzene

Physical state	Colorless, flammable liquid
Molecular weight	106.16 D
Boiling point	136.2°C
Autoignition	432°C
Flash point	18°C
LEL	6.7%
Henry's constant	6.6×10^{-3} (20°C)
Odor threshold	20–100 ppb (aromatic gasoline odor)
Solubility	Miscible in ethyl ether, ethanol, organic solvent
Organol-water constant (K_{ow})	3.15
Specific gravity	0.866
Vapor density	3.66 (air = 1)
Vapor pressure (20°C)	7 mm Hg

LEL, lowest explosive level.

Ethylbenzene is used in the chemical industry. It is produced by the Friedel-Crafts alkylation of benzene with ethylene, using an aluminum chloride catalyst. Most ethylbenzene is used as an intermediate chemical in the production of styrene (212). Among its other uses are as a general solvent in paint thinners, as a degreaser for paints and inks, and as a solvent in paints and lacquers. It is used also in the rubber and chemical manufacturing sectors.

Environmental Fate and Transport

The main environmental fate of ethylbenzene is volatilization into the atmosphere. Only small amounts of environmental ethylbenzene are found in water and soil, where it is slowly biodegraded. Ethylbenzene has low water solubility (152 mg per L at 20°C) and high vapor pressure (1.24 kPa at 20°C) (212).

Ethylbenzene is biodegradable in aquatic systems and soil. Soil bacteria metabolize ethylbenzene as a carbon source. Microbial oxidative degradation involves hydroxylation of the aromatic ring to 2,3-dihydroxy-1-ethylbenzene by soil bacteria. The biodegradation half-life is 2 days to 2 weeks (212). Ethylbenzene also undergoes aquatic anaerobic degradation by microorganisms in the presence of nitrates. Ethylbenzene undergoes atmospheric oxidation rapidly via photochemically produced free radicals. The atmospheric half-life ranges from 1 hour to a few weeks.

Exposure Sources

Mean concentrations of ethylbenzene in the atmosphere range from 0.74 to 100.0 µg per meter in urban areas, industries being the principal release points. Rural atmospheric concentrations are usually less than 2 µg per cubic meter (212). Industrial water concentrations up to 15 µg per L have been reported, whereas nonindustrial surface water contains less than 0.1 µg of ethylbenzene per L. Concentrations of ethylbenzene in uncontaminated groundwater are less than 0.1 µg per L. Higher concentrations have been found in contaminated groundwater from hydrocarbon releases, industrial facility releases, and waste disposal. Ethylbenzene is found also in effluents from wastewater and sewage treatment plants. Concentrations of ethylbenzene are elevated in urban areas owing to industrial releases.

The EPA studied ethylbenzene air concentrations in public buildings and found concentrations as high as 387 µg per cubic meter (90 ppb), which declined to 39 µg per cubic meter (9 ppb) several months after the buildings were completed (212). Ethylbenzene is emitted from carpet adhesives at a mean concentration of 6.4 µg per cubic meter, which corresponds to an emission rate of 77 ng per minute per square meter. Ethylbenzene is a common volatile organic chemical found in indoor building sites and new office buildings at levels ranging from 7.0 to 11.8 µg per cubic meter, as compared to 1.8 µg per cubic meter in the outdoor air (213,214).

Indoor air concentrations of ethylbenzene in randomly selected Canadian residences were studied in 1986, and mean concentrations were 6.46 µg per cubic meter in winter, 8.15 µg per cubic meter in spring, 4.35 µg per cubic meter in summer, and 13.97 µg per cubic meter in autumn (215).

Ethylbenzene also is contained in mainstream tobacco smoke, and blood concentrations of ethylbenzene can be measured in smokers as well as nonsmokers exposed to sidestream tobacco smoke (131). Combustion sources, including tobacco smoke, gasoline vapors, and other combustion products, contain ethylbenzene and increase human exposures to ethylbenzene.

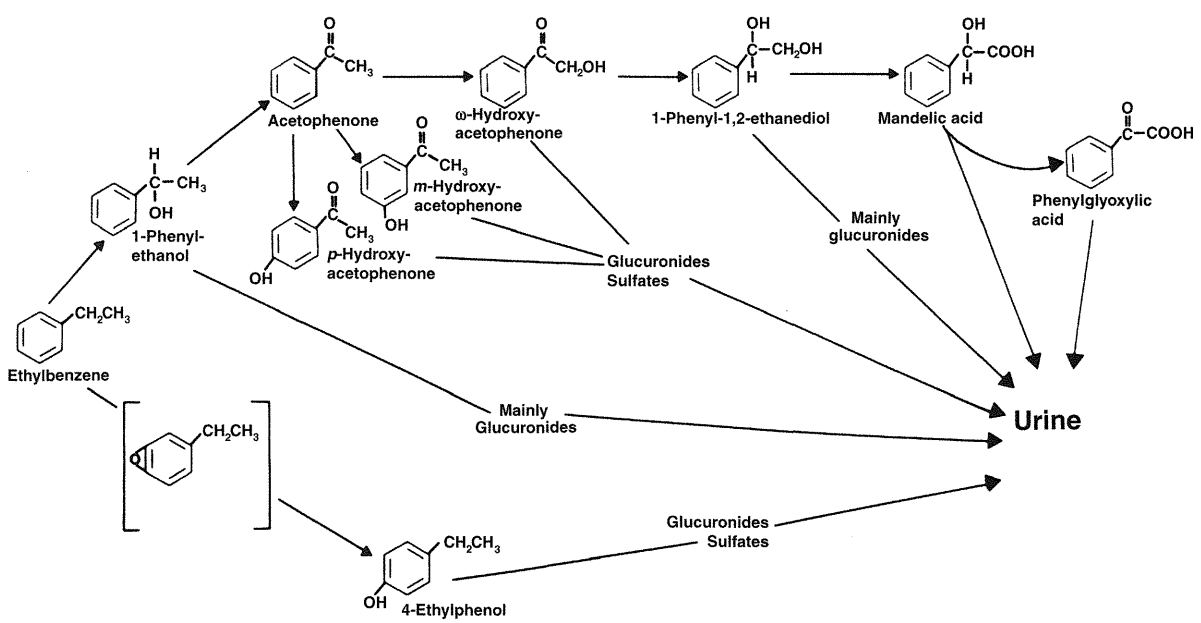


Figure 105-5. Ethylbenzene metabolism.

TABLE 105-18. Physiochemical properties of trimethylbenzene isomers

Property	1,3,5-Trimethylbenzene	1,2,3-Trimethylbenzene	1,2,4-Trimethylbenzene
Physical state	Colorless liquid	Colorless liquid	Colorless liquid
Molecular weight	120.19 D	120.19 D	120.19 D
Gasoline	1.32 wt%	0.73 wt%	4.9 wt%
Odor threshold			
In water	0.027 mg/L (0.00024–0.062 mg/L)	—	—
In air	0.1–1.0 mg/m^3	0.1–1.0 mg/m^3	0.1–1.0 mg/m^3
Vapor density	4.15	4.15	4.15
Specific gravity (20°C)	0.865	0.89	0.88
Conversion factor	1 ppm = 5 mg/m^3	1 ppm = 5 mg/m^3	1 ppm = 5 mg/m^3
Solubility	Miscible with ether, alcohol benzene; insoluble in water	Miscible with ether, alcohol benzene; insoluble in water	Miscible with ether, alcohol benzene; insoluble in water
Autoignition	1,022°F	878°F	959°F

Absorption, Metabolism, and Excretion

Ethylbenzene is readily absorbed via the inhalational, dermal, and GI routes. After systemic absorption, high concentrations are found in lungs, adipose tissue, kidneys, liver, and GI tract in those animals studied. Metabolism in animals is not the same as that in humans.

The metabolic transformation of ethylbenzene is shown in Figure 105-5. The main metabolic pathways involve oxidation of the side chains, and the main metabolites of ethylbenzene in humans are mandelic acid (64%) and phenylglyoxylic acid (25%) (171,216). Ethylbenzene is metabolized by the microsomal cytochrome P-450 enzyme system. The elimination half-life of ethylbenzene has been shown to vary from a few hours to 1 to 2 days, which is in agreement with the elimination of other volatile organic compounds, which have relatively resident times in the human body (216).

Clinical Toxicology

Ethylbenzene is absorbed via inhalation, ingestion, and dermal exposure, with dermal absorption in the range of 22 to 33 mg per square centimeter per hour (see Table 105-3) (64). Mucous membrane irritative effects from ethylbenzene occur at exposure to approximately 200 ppm.

Ethylbenzene possesses the potential to incite both acute and chronic toxic effects. Acutely, its vapors are an irritant to the mucous membranes and respiratory tract. Exposure to high vapor concentrations can result in CNS depression (217). Ingestion of ethylbenzene can cause GI irritation and vomiting and result in pulmonary aspiration.

Because ethylbenzene has hepatotoxic potential, liver functions should be monitored in those who are exposed to high concentrations. Rats and mice were exposed for 13 weeks to vapors of ethylbenzene. No chronically related histopathologic changes were observed and only insignificantly reduced weight gain was seen at an exposure of 1,000 ppm (212).

Epidemiologic studies conducted in groups who were occupationally exposed to mixtures of solvents including ethylbenzene have not been able to isolate the primary clinical toxicology picture of ethylbenzene alone. Reports from the 1970s indicate that at exposures exceeding the established occupational limits, human subjects report fatigue, drowsiness, headache, and irritation of the eyes and respiratory tract (217).

As a vapor, ethylbenzene is not well absorbed across the skin barrier. Although the absorption of liquid ethylbenzene across skin has been studied, data regarding skin permeability of this compound in humans are inconsistent with animal data.

Because most studies that evaluate ethylbenzene are designed also to evaluate other solvents, isolating data on ethylbenzene is difficult. Hence, little information is available on the long-term clinical toxic effects and the dose response or dose effect of ethylbenzene in humans.

Biological Monitoring

The determination of mandelic acid levels in urinary samples is a biomarker of exposure to ethylbenzene. A value of 1.5 g of mandelic acid per gram of creatinine is the post–work shift urinary level recommended as a BEI by the ACGIH (see Table 105-4). Measurement of phenylglyoxylic acid also is suggested for use as a biomarker (218).

Regulatory Aspects

The ACGIH TLV-TWA is 100 ppm (434 mg per cubic meter) and the STEL, 125 ppm (453 mg per cubic meter). The NIOSH's IDLH is 2,000 ppm.

TRIMETHYLBENZENE

Trimethylbenzenes are represented by the isomeric forms 1,2,3-trimethylbenzene (hemimellitene), 1,2,4-trimethylbenzene (pseudocumene), and 1,3,5-trimethylbenzene (mesitylene) (see Fig. 105-1). Trimethylbenzenes are a component of gasoline and vary from 0.73 to 4.9 wt%.

Trimethylbenzene is found as a component of dyes and pigments. Its vapors are irritating to mucous membranes, skin, eyes, and the respiratory tract and can cause CNS depression. All three isomers are flammable and, when heated to decomposition, emit acrid smoke and irritating fumes. This compound's physiochemical properties are summarized in Table 105-18.

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Clinical Environmental Health and Toxic Exposures

Second Edition

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